2011-12-19

Comparative Effectiveness of Alendronate and Risedronate on the Risk of Non-Vertebral Fractures in Older Women: An Instrumental Variables Approach: A Dissertation

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COMPARATIVE EFFECTIVENESS OF ALENDRONATE AND RISEDRONATE ON THE RISK OF NON-VERTEBRAL FRACTURES IN OLDER WOMEN: AN INSTRUMENTAL VARIABLES APPROACH

A Dissertation Presented

By

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Submitted to the Faculty of the

University of Massachusetts Graduate School of Biomedical Science, Worcester

in partial fulfillment of the requirement of the degree of

DOCTOR OF PHILOSOPHY

December 19, 2011

MAJOR SUBJECT

CLINICAL AND POPULATION HEALTH RESEARCH

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ACKNOWLEDGEMENTS

I would never have been able to finish my dissertation without the guidance of my advisor and committee members, help from friends, and support from my family.

I would like to express my deepest gratitude to my advisor, Dr. Becky Briesacher, for her excellent guidance, caring, patience, constant encouragement, and providing me with an excellent atmosphere for doing research. I would like to thank Drs. Jeroan Allison, Leslie Harrold, and George Reed, Fang Zhang for their constructive comments on my dissertation. Special thank goes to Drs. Jerry Gurwitz and Terry Field for offering me the opportunity to conduct my dissertation at the Meyers Primary Care Institute. I would also like to thank Drs. Jennifer Tjia and Robert Rood for working with me on some of my publications.

The faculty of the department of Clinical and Population Health Research have provided me with tremendous graduate education, research opportunity and economic support. My thanks also go to my fellow classmates for their support and encouragement during the past three years.

Finally, I would like to thank my parents, Wenfu Chen and Die Jin. They always stand by me through the good times and bad.

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ABSTRACT

Osteoporosis is a significant public health problem in the U.S. It not only affects the physical well-being of the older women but also creates a substantial financial burden for the health care system. The mainstay of osteoporosis medications is bisphosphonate treatment of which alendronate and risedronate are the most commonly prescribed in clinical practice. However, there have been no head-to-head randomized controlled trials (RCTs) evaluating the effects of these two bisphosphonates on fracture outcomes.

In the absence of RCTs, observational studies are necessary to provide alternative evidence on the comparative effectiveness between alendronate and risedronate on fracture outcomes. However, existing observational studies have provided inconclusive results partially due to residual confounding from unobserved variables such as patients' health status or behavior. IV analysis may be one method to address unmeasured confounding bias in observational studies. While it has not been applied in bisphosphonate research, it has been used in research on a variety of other prescription medications.

In this dissertation, we applied the IV approach with an IV, date of generic alendronate availability, to evaluate the comparative effectiveness between alendronate and risedronate using observational data. This dissertation improved current research in several ways. First, we extended the IV approach to research on bisphosphonates. Second, compared with the current observational studies on bisphosphonates, this dissertation may more accurately estimate the relative effects between alendronate and

risedronate because IV analysis is not subject to unmeasured confounding bias. Third, the study results extended the current evidence of the comparative effectiveness between the two most commonly prescribed bisphosphonates. Finally, we proposed and provided empirical evidence of a new IV that might be used for future prescription drug research.

The finding of this dissertation can be summarized from three aspects. First, we found that the evidence supported the validity of the date of generic availability as an IV in the study of bisphosphonates. Second, applying IV approach to study the comparative effectiveness of alendronate and risedronate, we found that alendronate and risedronate were comparable to reduce the risk of 12-month non-vertebral fractures in older women. Since generic alendronate is availability on the market while generic risedronate is not, promoting the use of alendronate may help reduce the healthcare cost and not sacrifice the clinical effectiveness. Finally, by comparing the proposed IV with a popular IV-physician preference, we found that both the calendar time IV based on the date of generic availability and the physician preference appeared to be valid. It might be practically easier to use the calendar time IV than the physician preference IV.

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1 CHAPTER I: INTRODUCTION

1.1 Specific Aims

The purpose of this dissertation was to investigate the comparative effectiveness of two bisphosphonates (alendronate and risedronate) on the risk of non-vertebral fractures in women 50 years of age or older using an instrumental variables (IV) approach.

Bisphosphonate therapy is the primary pharmacologic treatment for osteoporosis.[1, 2] Among all bisphosphonates, alendronate and risedronate are the most commonly prescribed in clinical practice.[3] While randomized control trials (RCTs) have shown that both agents reduce the risk of non-vertebral fractures, head-to-head trials comparing alendronate and risedronate are underpowered to study fracture outcomes[4] because a large sample size and a long follow-up are required to conduct such a trial. Observational studies can present alternative evidence for the relative effectiveness of the two drugs. However, they suffer from unmeasured confounding bias.[5] The IV approach,[6] recently introduced to medical research, is a methodological approach to reducing bias due to measured and unmeasured confounding that has been demonstrated to provide unbiased estimates of causal effect in observational studies.[7] Therefore, it presents an opportunity to conduct a head-to-head comparison between alendronate and risedronate using observational data and IV analysis.

The specific aims of this dissertation were as follows. **Aim 1:** We proposed a new calendar time IV (the date of generic availability) that might be useful for studying the comparative effectiveness of prescription drugs. We presented logical arguments and

examined empirical evidence to support the validity of the proposed IV through a study of bisphosphonates (alendronate and risedronate).

Aim 2: We examined the comparative effectiveness of alendronate vs. risedronate on the risk of 12 months non-vertebral fractures in women 50 years of age or older using the IV proposed in Aim 1.

Hypothesis: Compared to women initiating risedronate, those initiating alendronate had similar rates of 12 months non-vertebral fractures.

Aim 3: We examined whether two individual IVs can be used to address the same question in the same population. We compared the validity and performance of two IVs, the date of generic alendronate availability and the physician preference, in a case study of the comparative effectiveness of alendronate vs. risedronate on the risk of non-vertebral fractures in older women.

1.2 Background and Significance

1.2.1 Osteoporosis and Its Public Health Burden

Osteoporosis is "a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk for fracture".[8] With the aging of the United States (U.S.) population, osteoporosis is becoming a common and significant public health problem. First, it is estimated that 44 million Americans, approximately 55 percent of the population, 50 years and older have osteoporosis and low bone mineral

density (BMD).[9] Second, Stafford et al. observed a 4-fold increase in physician visits for osteoporosis in the U.S. within a decade, from 1.3 million visits in 1994 to 6.3 million visits in 2003.[1] Third, postmenopausal women are a particularly high risk population for this disease, accounting for more than 68% of the people age equal to or greater than 50 years who have osteoporosis and low BMD in the U.S.[9] Finally, despite high prevalence of osteoporosis in women, many women either do not receive or chose not to take osteoporosis medication. Yood et al. surveyed 236 women with confirmed diagnosis of osteoporosis from one health plan and found that 57.2 percent of them did not initiate osteoporosis medications within 3 months of diagnosis.[10]

One of the most important complications of osteoporosis is fractures including vertebral and non-vertebral fractures. Chrischilles et al. modeled aspects of lifetime osteoporosis impact and found that 54% women age 50 or older will have osteoporosis-related fractures during the course of their lives.[11] The economic burden resulting from treating osteoporosis and osteoporosis related fractures has been rising. Ray et al. estimated health care expenditures incurred by osteoporotic fractures in the U.S. in 1995 were $13.8 billion.[12] In 2003, Keen reported that approximate $17 billon has been spent annually on the management of osteoporosis in the U.S.[13] The costs of treating osteoporosis reached more than $19 billion in 2005 and are projected to increase more than 48% by 2050.[14]

1.2.2 Treatment of Osteoporosis

The increasing prevalence of osteoporosis along with the aging U.S. population and the substantial economic burden imposed by treating osteoporotic fractures has increased the interest in the pharmacologic treatment of osteoporosis. The Food and Drug Administration (FDA) has approved a number of medications for treatment of osteoporosis such as alendronate, risedronate, ibandronate, calcitonin, teriparatide, zoledronic acid and raxloxifene.[15] Hormone therapy has also been used to treat osteoporosis. However, the use of hormone therapy can increase the risk of breast cancer and cardiovascular disease in postmenopausal women.[16]

Bisphosphonates, including alendronate, risedronate, ibandronate and zoledronic acid, are the leading group of medications for treating osteoporosis.[1, 2] They decrease bone turnover and reduce resorption, which creates a positive bone balance at individual remodeling units and continuously improves bone mass.[17] Alendronate and risedronate are the most commonly prescribed bisphosphonates in clinical practice.[3] RCTs have consistently shown that compared with a placebo, alendronate and risedronate sustainably increase BMD at the spine and hip in a variety of populations including postmenopausal women with osteoporosis.[18-29] Moreover, high quality evidence from RCTs, and meta-analyses of RCTs and observational studies have shown that the two bisphosphonates prevent vertebral and non-vertebral fractures in women with postmenopausal osteoporosis. [4]

1.2.3 Comparative Effectiveness between Alendronate and Risedronate

Head-to-head trials have shown that alendronate has a greater effect than risedronate on increasing BMD and reducing bone turnover in postmenopausal women. In a trial conduced at 78 sites across the U.S., 1,053 women with postmenopausal osteoporosis were randomized to alendronate (n=520) and risedronate (n=513). Rosen et al.[30] found that patients taking alendronate had greater increases in BMD at hip trochanter (alendronate vs. risedronate: 3.4% vs. 2.1%, $P<0.001$) as well as all other BMD sites at 6 as well as 24 months from baseline than did patients taking risedronate. Compared with alendronate, risedronate also produced fewer reductions in all studied biochemical markers of bone turnover by 3 months. One year later, Bonnick et al.[31] reported the results from the first 2 years of the same trial. They found that compared with patients taking risedronate, those receiving alendronate had greater gain in BMD and reduction in bone turnover at 24 months.

While researchers have found strong correlation between BMD or biomarkers of bone turnover and fracture,[32] there is no conclusive evidence that the difference in BMD or in biomarkers of bone turnover can translate into a difference in fracture risk.[32-35] Therefore, evidence on the comparative effectiveness between alendronate and risedronate on the risk of non-vertebral fractures is necessary to determine which bisphosphonate is more effective in preventing fractures. However, there has been no head-to-head RCT designed to compare the two bisphosphonates on fracture outcomes for various reasons such as a substantial financial burden in conducting such a trial.

Furthermore, existing head-to-head trials, not designed for investigating the comparative effectiveness of the two bisphosphonates on the fracture risk, are either underpowered or too short of a duration to detect clinically significant differences in fracture incidences. [4, 15]

In the absence of head-to-head trials, observational studies provide alternative evidence on the relative effects of alendronate, compared to risedronate, on fracture outcomes. We reviewed the literature and found four observational studies comparing alendronate and risedronate on non-vertebral fracture incidences. However, the results from the four studies were inconsistent (**Table 1-1**), although they had similar study designs, statistical methods. Watts et al. [36] analyzed medical and pharmacy claims data comparing non-vertebral fractures between new users of alendronate (n=5,024) and risedronate (n=1,000) at 6 months, and alendronate (n=3,716) and risedronate (652) at12 months. They found a 54% risk reduction for risedronate vs. alendronate (HR =0.46; 95% CI, 0.02-1.06) at 6 months and a 59% risk reduction for risedronate vs. alendronate (HR = 0.41; 95% CI, 0.18 to 0.94) at 24 months.[36] Silverman et al. provided similar results in an even larger population with12,215 women taking risedronate and 21,615 taking alendronate.[3] They found that women on risedronate had a lower incidence of non-vertebral fractures than women on alendronate (HR=0.82; 95%CI: 0.68-0.98) through 12 months of therapy. However, the latest two cohort studies conducted by Cutis et al.[37] and Cadarette et al.[38] showed the difference in non-vertebral fracture risk between women on risedronate and alendronate was small and not statistically significant. For example, Cadarette reported a small difference in fractures risk between new recipients of

risedronate (n=8,718) and alendronate (n=21,007) with a hazard ratio of 1.07 (95%CI, 0.85-1.36) at 6 months, 1.01 (95%CI, 0.85-1.27) at 12 months and 0.96 (95%CI, 0.84-1.11) at 24 months.

Generally, there is sufficient evidence that both alendronate and risedronate increase BMD and reduce bone turnover with alendronate presenting a relatively stronger effect. However, head-to-head trials for the comparative effectiveness between alendronate and risedronate on fracture outcomes are lacking. Observational studies may provide an alternative source of evidence, but we found mixed results from observational studies given similar study design, statistical analysis and confounder adjustment. This suggests that further research is warranted. A possible reason for such inconsistent results and a potential method to solve such a problem will be discussed in the following section.

1.2.4 A Possible Reason for Inconsistent Results

Despite using similar observational study designs, statistical analyses and confounding adjustment, inconsistent results appeared in the recent studies regarding the comparative effectiveness between alendronate and risedronate on the risk of fracture outcomes (discussed before). [3, 36-38] One possible explanation for such an inconsistency is that observational studies may suffer from confounding bias since participants are not randomized to treatment. Many of the reasons that patients are prescribed a drug are the same reasons that determine how well patients do in the outcome (confounding by indication).[39-42] As a result, evidence obtained from observational studies about the

treatment and outcome relationship may be subject to confounding bias. Methods such as conventional regression and propensity score[43] analysis have been developed to address measureable confounding; however, residual confounding may remain from unmeasured factors. [3, 36, 38]

1.3 IV Approach

1.3.1 Background

IV analysis, widely used in economics, is one method for addressing both measured and unmeasured confounding [44] with observational data. It is a technique enabling researchers to take advantage of observational data such as claims data and registry data to more correctly estimate the effectiveness or safety of a medication even if unmeasured risk factors are present. **Figure 1-1**, adopted from Brookhart et al.,[45] illustrates this technique.[46] The central idea of IV analysis is to find a variable that has a causal effect with the treatment assignment, in this case a prescription drug, but is not related to the outcome, except through its relationship with the treatment assignment. A good IV should satisfy two key assumptions. First, the IV should be strongly related to the treatment assignment. Second, the instrument should not be correlated with measured and unmeasured confounders and only related to the outcome through the treatment assignment (exclusion criteria). This means that the IV should neither be related to risk factors of the outcome (the uppermost pathway [dash line] in **Figure 1-1**) nor have direct effect on the outcome (the lowermost pathway [dash-dot line] in **Figure 1-1**). Therefore,

it is only related with the outcome through the treatment assignment (the middle pathway [dot line] in **Figure 1-1**).

1.3.2 Examples of Valid IVs

A special example of a valid IV is the randomization process,[47] for example coin toss, in a randomized trial for prescription drugs. It is a strong IV because the treatment assignment is solely dependent on the coin toss, which meets the first assumption. Second, the likelihood of receiving treatment based on the process, tossing a coin, is independent of patient characteristics and it is not related to the outcome, except through treatment. This meets another IV assumption.

IV analysis in observational (i.e. non-randomized) studies attempts to mimic the randomization process. In such an example, Brookhart and colleagues[48] were comparing Cyclooxygenase 2 (COX-2) inhibitor and non-selective non-steroidal anti-inflammatory drugs (NSAID) use and risk of gastrointestinal (GI) complications. The investigators calculated a measure of physician preference for type of drug and used it as an IV. They argued that patients will be more likely to receive a COX-2 inhibitor if their physician prefers these agents. Furthermore, this prescribing preference supersedes an individual patient's indication for this medication, and patients will not select physicians based on this prescribing preference. These arguments suggest that physician's treatment preference may serve as a viable IV.

1.3.3 IV Analysis

One of the methods of calculating IV estimator for a dichotomous treatment assignment and outcome is through two stage least squares (2SLS).[44] In general, two simultaneous linear equations are built. The first equation models the probability of receiving a treatment assignment given the IV and measured confounders and outputs the predicted value. The second equation models the outcome given the predicted value of treatment assignment and measured confounders. If we consider randomization process as an IV, the IV estimator will be the same as results estimated by regression analysis. The detailed discussion of IV estimator will be presented in the later sections.

1.3.4 Application of IV Analysis in Prescription Drug Research

Research for comparing the safety and effectiveness of prescription drugs may be a fruitful area for the application of IV analysis. This method is gaining popularity in prescription drug research. Comparing the number of published articles from 2001 to 2003, the number of articles regarding applying IV analysis in prescription drug research increased 4-fold from 2004 to 2006 and 8-fold from 2007 to 2009.[46] IVs may be derived from several levels (regional variation, [49-56] facility prescribing patterns, [57-59] physician preference, [60-63] patient history/financial status, [64-66] calendar time [67-70] and others) and have been applied in post-market comparative effectiveness research on a variety of prescription medications.[45, 62, 63] For instance, Brookhart et al.[48] calculated a measure of physician preference for COX-2 inhibitor over NSAID and used it as an IV in comparing the risk of gastrointestinal complications between the two types of medications. They

analyzed the data using both the IV approach and multivariate regression analysis, and found that effect estimates from the IV approach were consistent with those from RCTs, while results from multivariate analysis were not due to residual confounding from unmeasured variables.

1.4 Research Design and Methods

1.4.1 Data Source

This dissertation used the Medstat MarketScan Commercial Claims and Encounters (CCE) and Medicare Supplemental Database (Ann Arbor, MI). Data were available for 2005-2009 and partially for 2010. The MarketScan database captures the largest convenient sample of over 73 million unique patients. Since 1996, it has collected information mostly from large employers in the U.S.[71] This nationwide database contains over 500 million claim records per year from individuals with employer-sponsored health insurance. Information captured in the database includes patient demographics, detailed enrollment, inpatient services, physician encounters and pharmacy claims. Scientific studies based on this data source have been reported in more than 100 peer-reviewed articles.[71]

The MarketScan databases offer advantages over raw administrative claims because data files undergo validity and editing procedures to ensure high quality and consistency in fields across the years.[72] The data are evaluated against population norms, previous year summaries, and validated data subsets. Outliers are flagged and reviewed

for coding or processing errors. Encounter data are audited at the health plan level, and plans submitting incomplete data are excluded. Diagnostic and procedural codes are compared against validity algorithms and set to missing values if inconsistent.

1.4.2 Organization of the Databases

The MarketScan databases include fours files: 1) medical and surgical claims, 2) aggregated populations table, 3) outpatient pharmaceutical claims table, and 4) annual enrollment summary table and enrollment detail table. The medical and surgical claims contain four tables (inpatient admission table, facility header table, inpatient services table and outpatient services table). The inpatient admission table summarizes information on hospital admission after identifying all of the encounters or claims associated with an admission. It also includes data such as the principal procedure, principal diagnosis, Major Diagnosis Category (MDC), and Diagnosis Related Group (DRG). The inpatient services table records an individual's facility and professional encounters and services through an inpatient admission. The outpatient services table contains information on encounters and claims for services that appear in a doctor's office, hospital outpatient facility or emergency room. The facility header table contains complete information on facility claims.

The aggregated populations table is used to generate quarterly counts of individuals with medical, surgical and outpatient pharmaceutical claims in order to calculate aggregated rate-based statistics. The outpatient pharmaceutical claims data are available for individuals who have an outpatient dispensing of a medication. A large

portion of the individuals on the medical and surgical claims table can be found on this table. The enrollment tables can be lined to the medical and surgical claims and outpatient pharmaceutical table. They provide individual-level continuous enrollment records with demographic information.

1.4.3 Study Designs and Populations

Aim 1

We conducted retrospective cohort studies. **Figure 1-2** shows the sample selection strategy. We selected women, 50 years of age or older, who had ≥1 OP diagnosis between 2007 and 2009 (n=729,978). We further restricted the population to women who had continuous enrollment and ≥1 Fracture Risk Assessment Tool (FRAX) risk factors[73, 74] but no diagnoses of Paget disease (ICD-9-CM code: 731.0) or malignancy (ICD-9-CM: 140-208). We then identified 116,359 women who initiated an oral alendronate (10mg or 70mg) or risedronate (5mg or 35mg) or no OP treatment within 90 days after the index date (date of the first OP diagnosis). We excluded women who had any OP medications within 12 months before the index date (n=66,564). The final sample included three groups: 1) women initiating an alendronate (n=3,717), 2) women initiating a risedronate (n=1,625) and 3) women with no OP treatment (n=37,948).

Aim 2 and Aim 3

We conducted a retrospective cohort study and adopted a new user design[75, 76] for both studies. **Figure 1-3** shows the sample selection strategy. We selected women, 50 years of age or older, who had enrollment information between 2007 and 2009 (N=8,034,624). We then identified women who initiated oral alendronate (10mg or 70mg) or risedronate (5mg or 35mg) during the time period and had continuous enrollment before and after the index date ─ date of initiation of an alendronate or risedronate (N=360,857). Individuals were excluded if: 1) they had a bisphosphonate within 12 months before the index date (N=249,048); and 2) they had a diagnosis of Paget's disease (ICD-9-CM code: 731.0) or malignant neoplasm (ICD-9-CM: 140-208) within one year before the index date (N=11,496). The study sample for **Aim 2** included 100,313 women, among which 79,370 initiated an alendronate and 32,439 initiated a risedronate. Finally, for **Aim 3** we restricted our sample to women who had information on physician preference. The analytic sample included 3,190 women, among whom 2,332 initiated an alendronate and 858 risedronate.

1.4.4 Measures

Outcome Variables

The main outcome variable was an indicator of non-vertebral fractures (including hip, wrist/forearm, humerus, clavicle, pelvis, leg fracture). It was identified during the first year (3, 6 and 12 months) following the index date. We used diagnostic and

procedure codes from claims to identify non-vertebral fractures based on approaches described by previous research [38, 77, 78] (**Table 1-2** for ICD codes). Using claims data to identify fracture outcomes will achieve 90% sensitivity if medical records are the reference standard.[77]

Instrumental Variables

We used IV analysis with the date of generic alendronate availability (February 1, 2008) as an IV. The variable was dichotomized with zero indicating the period before February 1, 2008 and one otherwise. We consider the date of generic alendronate availability a valid IV because it satisfies assumptions of a valid IV (detailed discussion in **Chapter II**). First, the availability of generic alendronate influences medication choice. The use of alendronate increases after its generic version is on the market due to drop in price. Second, the date of generic alendronate availability is not related to measured and unmeasured risk factors of non-vertebral fractures. Patient characteristics, such as age, frailty and healthy behaviors that may affect their medication choices are independent of this date.

In Aim 3 we also used a physician preference IV that has been applied in several studies examining the comparative effectiveness of prescription drugs (i.e. atypical vs. typical antipsychotics).[45, 61, 63, 79] We adapted a method based on Brookhart et al. to measure physician preference - namely the most recent new bisphosphonate prescription for a prescriber's patient other than the present patient.[45]

Covariate Measures

We measured four domains of variables: demographic characteristics, osteoporosis-related variables, co-morbidity and concomitant medications, and health services utilization (see **Table 1-3** for detail). Demographic characteristics including age were defined at the index. The rest of the domains of variables were measured during the 12 months period before the index date. Osteoporosis related variable included diagnosis of osteoporosis. For co-morbidity, we calculated a co-morbidity risk score from the Diagnostic Cost Group Hierarchical Condition Category (DCG/HCC) classification system (DxCG, Boston, MA). The DCG/HCC risk adjuster creates a single score for each person based on the presence of 189 medical conditions in the diagnosis fields of claims records. For medications, we first identified specific drugs that may cause OP; may treat or prevent osteoporosis and may be associated with fractures (**Table 1-3** for detailed drug information). We also measured hospitalization and use of mammogram as a proxy for a healthy behavior.

1.4.5 Statistical Analysis

Descriptive Statistics (Aim 1, Aim 2, Aim 3)

We presented means and standard deviations for continuous variables and proportions for discrete variables. We compared means using t-tests and proportions using Chi-square tests and Fisher's exact tests. We examined the distributions of patient characteristics by the original treatment (alendronate and risedronate) and then by the two

levels of the IV (before and after February, 2008). The reduction in the imbalance of patient characteristics due to the usage of the IV was presented. We also graphed the trend of using alendronate before and after it turned generic.

Conventional Analysis (Aim 2 and Aim 3)

We examined the crude association between study bisphosphonates and non-vertebral fracture outcomes using simple linear regressions. We also conducted multiple linear regressions to assess the association adjusting for variables described in the covariates section. We reported risk differences (RDs) from the linear regressions. The reason we chose linear regression instead of logistic regression was that linear reports RD which can be used to compare results between the conventional analyses and the IV analyses.[48]

Two Stage Least Squares (Aim 2 and Aim 3)

We also examined the association between study bisphosphonates and non-vertebral fracture outcome using an IV analysis. The 2SLS has been used in the IV analysis with a binary treatment assignment and outcome by many researchers. It involved two simultaneous multiple linear regression models. In general, in the first stage, we regressed the treatment assignment on the IV and other measured confounders. In the second stage, we regressed the outcome on the predicted values of treatment assignment obtained from the first stage and other measured confounders.

First Stage Model

The first stage model is specified as

Equation (1)

$$E[T_i \mid IV_i, X_i] = Pr(T_i=1 \mid IV_i, X_i) = \alpha_0+\alpha_1 IV_i+\sum_{j=2}^{m} \alpha_j X_{ji}$$

where E[T|IV] indicates the expected value of the treatment assignment for the i^{th} patient given the IV after controlling for measured covariates. T equals to 1 when the patient receives an alendronate and 0 otherwise. IV is the date of generic alendronate availability. It equals to 1 when the date is after February, 2008 and 0 otherwise. X is a vector of measured covariates. $\widehat{\alpha_1}$ estimates the increase in the probability of receiving an alendronate after the date of generic alendronate availability.

Second Stage Model

The second stage predicts the probability of the outcome given the probability of receiving an alendronate estimated from the first stage. The model is specified in equation 2.

Equation (2)

$$E[Y_i \mid IV_i, X_i] = Pr(Y_i=1 \mid Pr(T_i=1 \mid IV_i, X_i), X_i) = \beta_0+\beta_1 Pr(T_i=1 \mid IV_i, X_i) + \sum_{j=2}^{m} \beta_j X_{ji}$$

Equation (3)

IV estimator = $\widehat{\beta_1}$ =

$$\frac{\Pr\left(\mathrm{Yi}=1|\Pr\left(\mathrm{Ti}=1|\mathrm{IVi}=1,\mathrm{Xi}\right),\mathrm{Xi}\right)-\Pr\left(\mathrm{Yi}=1|\ \Pr\left(\mathrm{Ti}=1|\mathrm{IVi}=0,\mathrm{Xi}\right),\mathrm{Xi}\right)}{\Pr\left(\mathrm{Ti}=1|\mathrm{IVi}=1,\mathrm{Xi}\right)-\Pr\left(\mathrm{Ti}=1|\ \mathrm{IVi}=0,\mathrm{Xi}\right)}$$

Equation (4)

IV estimator =

$$\frac{\mathrm{E}[\mathrm{Y}|\mathrm{IV}=1]-\mathrm{E}[\mathrm{Y}|\mathrm{IV}=0]}{\mathrm{E}[\mathrm{T}|\mathrm{IV}=1]-\mathrm{E}[\mathrm{T}|\mathrm{IV}=0]}$$

In the equation (2), Y represents the outcome, an indicator of non-vertebral fracture. It equals to 1 when a patient has at least one non-vertebral fracture and 0 otherwise. $\widehat{\beta_1}$ (Equation (3)) is the IV estimator for equation (2). Equation (4) is the simplified version of equation (3) and it represents the difference in the outcome given the IV divided by the difference in the treatment probability given the IV. It estimates the adjusted risk difference in probability of the outcome between the two hypothetical cases, predicted by the IV. Therefore, it represents the causal effect of the treatment on the outcome. When the IV perfectly predicts the treatment assignment, the IV estimator is equal to the risk difference in the outcome between the two medications.

Performance of IVs and Compare Two IVs (Aim 1 and Aim 3)

In Aim 1 we examined the performance of the proposed IV (detailed discussion in **Chapter II**) and in Aim 3 we compared the performance of the two IVs (detailed

discussion in **Chapter IV**) based on empirical evidence of the assumptions of a valid IV. First, we examined the strength of the IV by reporting F statistics from the first stage of the 2SLS. F statistic ≥ 10 indicates a strong IV[80] and a greater F statistic indicates a stronger IV. Second, we assessed the ability of IVs to balance measured patient characteristics. A stronger IV should be associated with fewer measured confounders.[81] We also assessed the balance of patient characteristics by reporting standardized differences between the original treatment and between the two levels of the IV. The standardized difference is specified in **equation (5)** and **(6)** for means and proportions.[82] In **equation (5)**, d represents the standardized difference; $X_{treatment1}$ and $X_{treatment2}$ are the sample mean of the covariate in treatment 1 and treatment 2 respectively and $S^2_{treatment1}$ and $S^2_{treatment2}$ are the sample variance of the covariate in treatment 1 and treatment 2 respectively. In **equation (6)**, d represents the standardized difference and $P_{treatment1}$ and $P_{treatment2}$ are the sample proportion of the covariate in treatment 1 and treatment 2 respectively.

Equation (5)

$$d = \frac{(\overline{x}_{treatment\ 1} - \overline{x}_{treatment\ 2})}{\sqrt{\frac{s^2{}_{treatment\ 1} - s^2{}_{treatment\ 2}}{2}}}$$

Equation (6)

$$d = \frac{(\hat{p}_{treatment\ 1} - \hat{p}_{treatment\ 2})}{\sqrt{\frac{\hat{p}_{treatment\ 1}(1 - \hat{p}_{treatment\ 1}) - \hat{p}_{treatment\ 2}(1 - \hat{p}_{treatment\ 2})}{2}}}$$

Finally, the assumption that a valid IV should not directly cause a patient outcome is not verifiable. We adopted a method by Newhouse and McClellan[6] to indirectly verify this assumption. We assessed whether the IVs were able to keep balance of the distribution of the short-term outcomes (i.e. 3-month non-vertebral fracture) that cannot be affected by the medical intervention (bisphosphonates).

1.5 Summary and Innovations

In summary, osteoporosis is a significant public health problem in the U.S. It not only affects the physical well-being of the older women but also creates a substantial financial burden for the health care system. Effective pharmacologic treatment for osteoporosis will help improve the health of women with osteoporosis as well as prevent or attenuate future costly procedures associated with osteoporotic fractures in this population. The mainstay of osteoporosis medications are bisphosphonates of which alendronate and risedronate are the most commonly prescribed in clinical practice. However, there has been no head-to-head trial evaluating the effects of these two bisphosphonates on fracture outcomes.

In the absence of RCTs, observational studies are necessary to provide alternative evidence on the comparative effectiveness between alendronate and risedronate on fracture outcomes. However, existing observational studies have provided inconclusive results partially due to residual confounding from unobserved variables such as patients' health status or behavior. IV analysis may be one method to address unmeasured confounding bias in observational studies. While it has not been applied in

bisphosphonate research, it has been used in research on a variety of other prescription medications.

In this dissertation, we applied the IV approach with an IV, date of generic alendronate availability, to evaluate the comparative effectiveness between alendronate and risedronate using observational data. This dissertation improved current research in several ways. First, we extended the IV approach to research on bisphosphonates. Second, compared with the current observational studies on bisphosphonates, this dissertation may more accurately estimate the relative effects between alendronate and risedronate because IV analysis is not subject to unmeasured confounding bias. Third, the study results extended the current evidence of the comparative effectiveness between the two most commonly prescribed bisphosphonates. Finally, we proposed and provided empirical evidence of a new IV that might be used for future prescription drug research.

Table 1-1: Estimates of the Comparative Effectiveness of Alendronate vs. Risedronate on the Risk of Non-vertebral Fractures from Four Existing Observational Studies

Authors and publication year	Population	Methods	Adjusted variables	Adjusted HR and 95% CI (Risedronate vs. alendronate)
Watt et. al. 2004[36]	6 mo: Alendronate (n=5,307) Risedronate (n=1,000) 12 mo: Alendronate (n=3,716) Risedronate (n=652)	Cox-proportion regression	Age, sex hormone therapy use, prior fragility fracture and number of concomitant medications in the pretreatment period	6 mo: 0.46 (0.2-1.06) 12 mo: 0.41 (0.18-0.94)
Silverman et. al. 2007[3]	Alendronate (n=21,615) Risedronate (n=12,215)	Cox-proportion regression	Age, estrogen use, number of medications, rheumatoid arthritis, history of non-vertebral fractures	6 mo: 0.81 (0.65-1.00) 12 mo: 0.82 (0.68-0.98)
Curtis et. al. 2009[37]	Alendronate (n=12,956) Risedronate (n=6,107)	Cox-proportion regression	Age, number of outpatient visits, Charlson co-morbidity index, use of screening tests including BMD, prior fracture, and use of prior estrogen, glucocorticoids and non-bisphosphonate osteoporosis medications	12 mo: 1.12 (0.70-1.79)

Cadarette et. al. 2009[38]	Alendronate (n=21,007) Risedronate (n=8,718)	Cox-proportion regression	Propensity score + age, race, diagnosis of osteoporosis, previous vertebral fracture, and previous non-vertebral fracture, stratified by state	6 mo: 1.07 (0.85-1.36) 12 mo: 1.01 (0.85-1.21) 24 mo: 0.96 (0.84-1.11)

Table 1-2: Codes for Non-vertebral Fractures

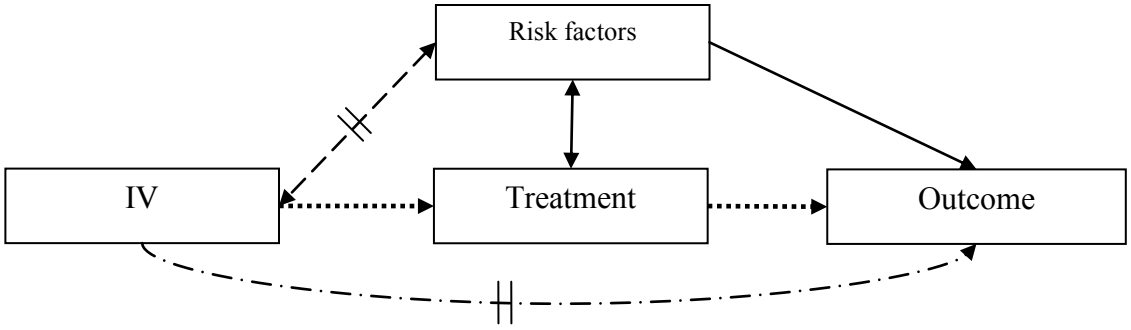
Fracture site	ICD-9	ICD-9 procedures	CPT
Wrist	813.x, 813.4x, 813.5x,	79.02, 79.12, 79.22, 79.32	25600, 25605, 25611, 25620
Hip	820.x, 821.x	79.x5, 79.05, 79.15, 79.25, 79.35,	27230-27248
Humerus	812.20, 812.21, 812.30, 812.31,	78.12, 78.52, 79.11, 79.21, 79.31	24500, 24505, 24515, 24516

Table 1-3: Variable Definition and Coding

Variable	Definition	Coding
Demographics		
Age	Age at the time of the index date	Will be categorized
Osteoporosis related measures		
Osteoporosis diagnosis	ICD-9 code 733.0x	Dichotomous
Non-vertebral Fractures history	See table 1	Dichotomous
Co-morbidity conditions	DCG/HCC	Original score or quartiles
Drugs that cause OP		
Glucocorticoid	Any pharmacy claim	Dichotomous
PPI	Any pharmacy claim	Dichotomous
H2 Inhibitor	Any pharmacy claim	Dichotomous
Thyroid drug	Any pharmacy claim	Dichotomous
Drugs that treat/prevent OP		
Vitamin D	Any pharmacy claim	Dichotomous
Estrogen	Any pharmacy claim	Dichotomous
SERMs	Any pharmacy claim	Dichotomous
Parathyroid Hormone	Any pharmacy claim	Dichotomous
Calcitonin		
Drugs associated with fracture		
Benzodiazepine	Any pharmacy claim	Dichotomous
SSRI/Non-SSRI	Any pharmacy claim	Dichotomous
Anticonvulsant	Any pharmacy claim	Dichotomous
Hypnotics	Any pharmacy claim	Dichotomous
B blocker	Any pharmacy claim	Dichotomous
Thiazide	Any pharmacy claim	Dichotomous
NSAIDS/Cox-2 inhibitor	Any pharmacy claim	Dichotomous
Geography		
North Central		
Northeast		
South		
West		
Health plan type		
Comprehensive		
HMO		
POS		
PPO		
Health service utilization		
Hospitalization	Hospital claim	Dichotomous
Mammogram	CPT code	Dichotomous

OP= osteoporosis; DCG/HCC= Diagnostic Cost Group Hierarchical Condition Category; SSRI=selective serotonin reuptake inhibitor; NSAIDS=non-steroidal anti-inflammatory drug; Cox-2=cyclooxygenase-2; HMO=Health Maintenance Organization; POS=Point of Service; PPO=Preferred Provider Organization

Figure 1-1: Instrumental Variable Approach



Uppermost pathway: IV is not related with risk factors of the outcome

Middle pathway: IV is only correlated with the outcome through treatment assignment.

Lowermost pathway: there is no direct effect on the outcome

The two parallel lines means no association.

Adopted from Brookhart et. al.

Figure 1-2: Sample Selection Strategy for Aim 1*

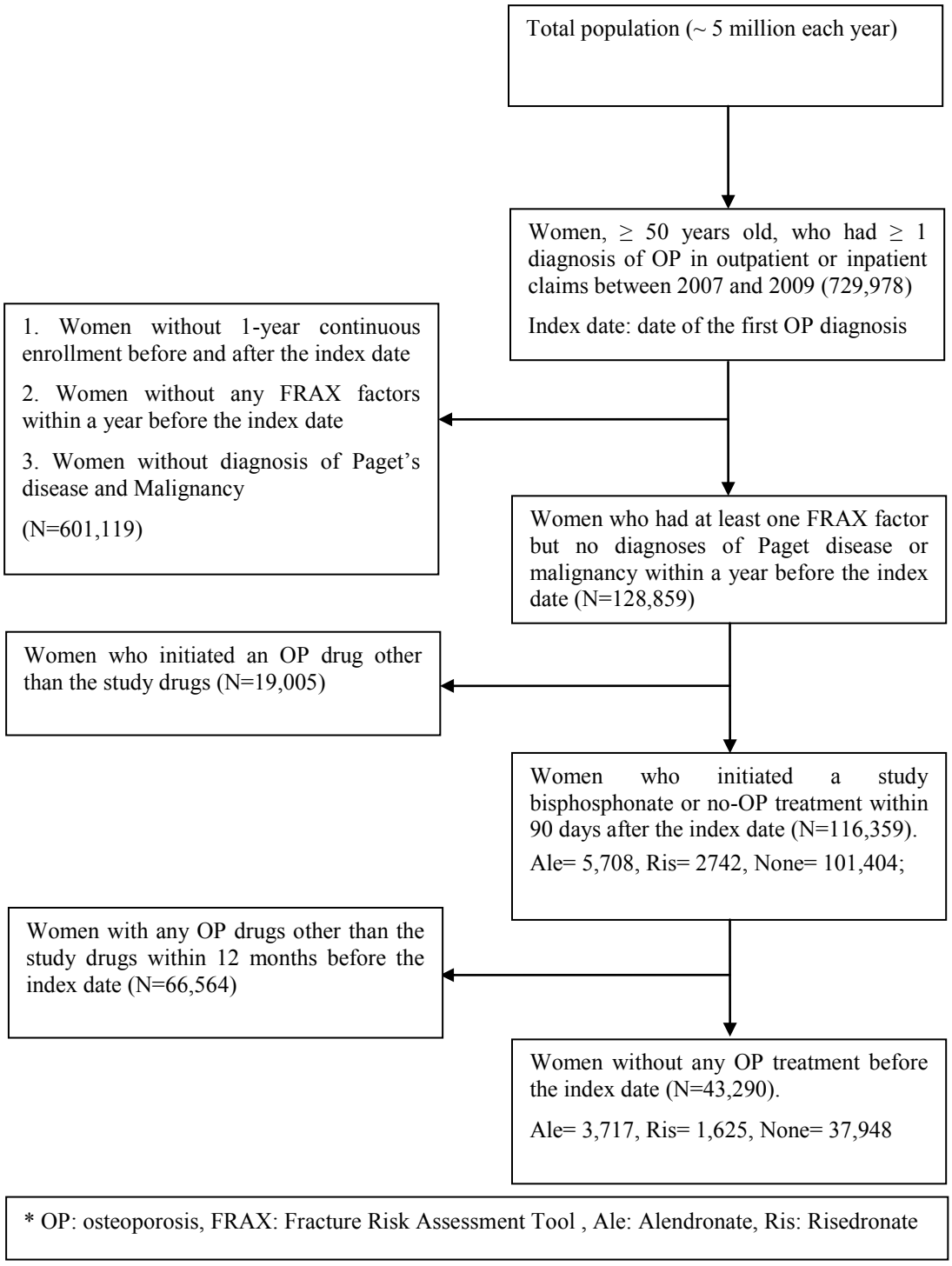
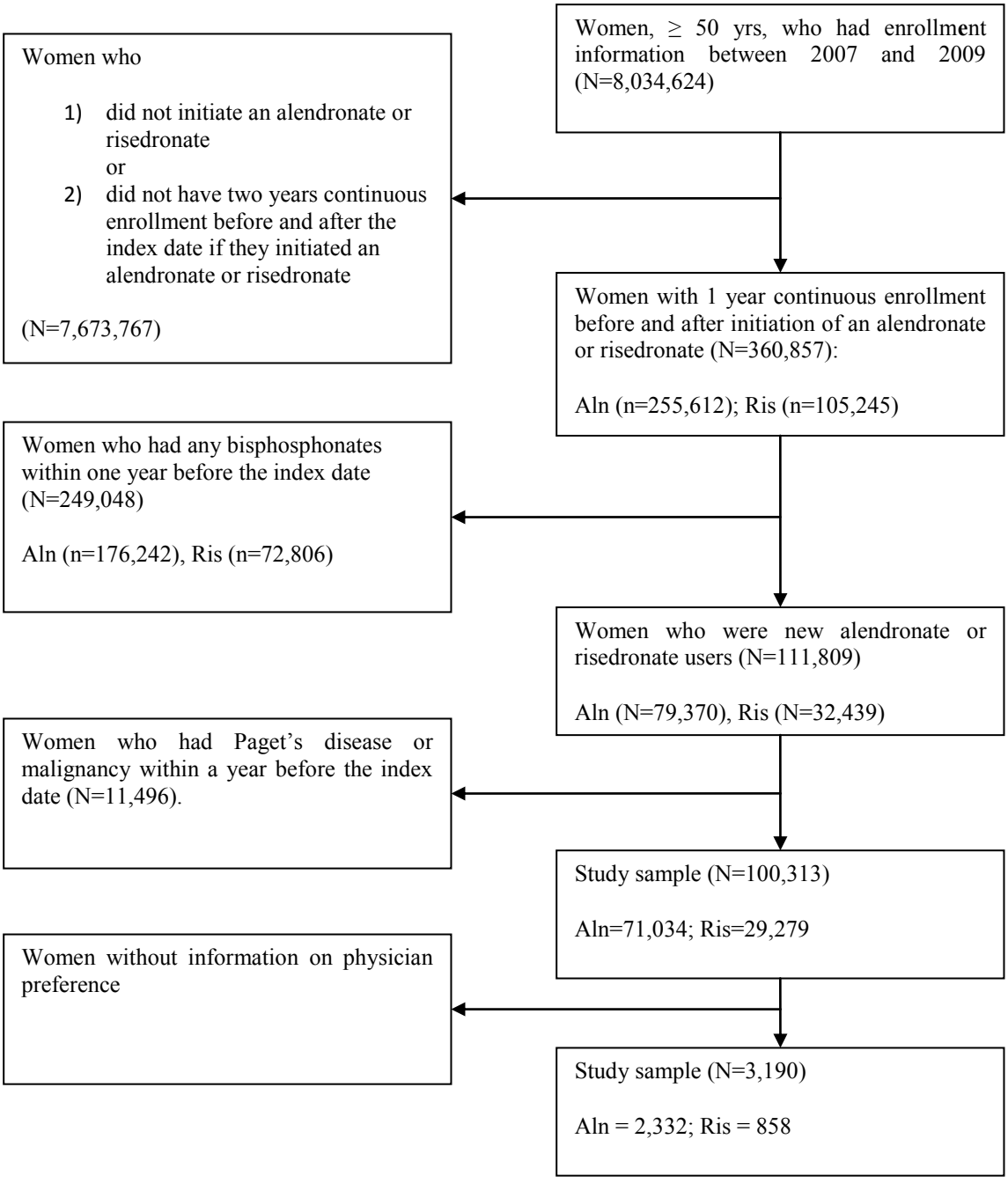


Figure 1-3: Sample Selection Strategy for Aim 2 and 3*



***Aln=Alendronate, Ris =Risedronate**

2 CHAPTER II: DATE OF GENERIC AVAILABILITY - A POTENTIAL INSTRUMENTAL VARIABLE IN THE COMPARATIVE EFFECTIVENESS RESEARCH OF PRESCRIPTION DRUGS

2.1 Introduction

Observational studies using large administrative data can provide essential evidence for the comparative effectiveness of prescription drugs.[83] However, observational studies may produce biased results due to unmeasured confounding[84] (e.g. administrative data do not generally have information on important factors such as healthy behaviors and frailty). The instrumental variables (IV) approach has been proposed as one way to address both measured and unmeasured confounding.[6] The main challenge is finding a credible IV[47] that is: 1) highly associated with the treatment choice and 2) independent of measured and unmeasured confounders, and has no direct effect on the outcome (two assumptions).[81, 85]

In this paper, we provide the theoretical foundation and empirical evidence for a new IV that may be useful in comparative effectiveness studies of prescription drugs---namely, the date that generic products become available. In general, the patent expiration of the brand name medication is followed by the availability of generic versions that are substantially less costly and may increase treatment use. This natural variation in treatment choice may provide a valid IV. We also tested the validity of this IV using the patent expiration of the bisphosphonate alendronate (brand name Fosamax) and two comparison groups: 1) individuals not taking any osteoporosis (OP) treatment, and 2) individuals taking an alternative bisphosphonate risedronate (brand name Actonel), which is still under patent protection. The reasons for selecting these comparisons are: 1) alendronate is an example of a popular "blockbuster" drug that became available as

generic in February 2008, 2) the no OP treatment group provides an opportunity to explore the performance of the IV under the scenario of a "placebo" control; 3) the risedronate treatment group provides allows us to assess the performance of the IV under a comparative effectiveness scenario. Finally, we discuss the potential implications of this IV in prescription drug research.

2.1.1 Theoretical Foundation of the Proposed IV

The validity of an IV depends on its ability to satisfy the two restricted assumptions. It is unnecessary to conduct the IV analysis if we do not have a strong theoretical foundation to support the validity of the proposed IV.[81]

We posit that the date of generic availability satisfies the first IV assumption, namely that the IV is highly associated with the treatment choice, according to the following rationale. After a brand name medication loses its patent protection, the use of the generic equivalents can occur quickly and the effect can be large. Empirical evidence supporting this statement comes from two sources. First, the Hatch-Waxman Act allows generic manufacturers to initiate clinical tests for the generic product before expiration of the patent.[86] This speeds up the entry of generics to within several months after the original drug's patent expiration.[86] Empirical studies have shown that the generic share of all prescriptions has been rising steadily in the last few decades: from 19% in 1984 to 75% of all prescription drugs by 2009 [87]. This growth in generic utilization may be due to 1) increase in generic availability of popular "blockbuster" drugs – drugs with annual sales exceeding $1 billion, such as Zocor (simvastatin) and Plavix (clopidogrel) which

expired in 2006; Ambien (zolpidem), Norvasc (amlodipine) and Protonix (pantoprazole) 2007; Fosamax (alendronate) 2008 and Prevacid (lansoprazole) 2009 [87]; and 2) expansion in drug coverage for generic products and lower co-pay incentives for generic utilization[87].

Second, increases in the use of a brand name drug and its generic equivalents can also come from reductions in use of other brand name drugs indicated for the same medical conditions. Berndt and Aitken studied intermolecular substitution following the loss of patent protection of Zocor (simvastatin), a brand name cholesterol-lowering statin.[87] They argued that sales of a medication (brand plus generics) might increase following patent expiration whereas other patent protected branded drugs treating the same medical condition might fall. In 2007, a year after the generic availability of Zocor (simvastatin), Lipitor was still under patent protection. Total monthly Zocor and its generic simvastatin prescriptions increased from 2.6 million in 2006 to 4.8 million by the end of 2007. In contrast, sale of Lipitor fell 12% in the same period. They found that the increase in total dispensing of Zocor and generic simvastatin came from two sources: 1) patients switched from Lipitor and 2) patients initiated Zocor or its generic simvastatin.

We also argue that the date of generic availability satisfies the second IV assumption of no direct or indirect association with the patient outcome except through treatment assignment. The date of generic availability is a calendar time IV so any residual confounding can only occur by factors that vary at the exact same time as the IV. For instance, changes in insurance status must vary at the same time as the study

medication goes off patent or, any changes in healthy behaviors must coincide with the date of generic availability. Similarly, the date of generic availability is unlikely to have direct effect on patient outcomes (i.e. fracture). Furthermore, seasonal trends may impact patient outcomes such as the mortality and fracture rate; however, they can be accounted for in the statistical model and by including enough data for the pre and post period of the generic availability.

2.1.2 Rationale for Testing for the Validity of the IV

In the demonstration studies, we will test for the validity of the IV wherever possible. For the first assumption, it is shown in the literature that a strong IV should explain variation of the treatment choice.[6] If we regress the treatment assignment on the IV and measured covariates, a strong IV should yield a partial F statistic greater than or equal to 10.[80] However, in theory the second assumption is not verifiable. Researchers have suggested several indirect methods to support this assumption. For instance, Brookhart et al. have shown that a valid IV should reduce the imbalance of patient characteristics by the original treatment assignment.[81] Furthermore, Newhouse and McClellan have shown that a valid IV (differential distance) should be able to restore balance in short-term outcomes (i.e. one-day mortality) that cannot be affected by the medical intervention (catheterization).[6]

In the case of the bisphosphonates, alendronate and risedronate have a delayed mechanism of action, which can be used for assessing the validity of the IV. These agents cannot impact short-term non-vertebral fracture rates (i.e. within 3 months of

initiation) so a valid IV should be able to impose balance on 3-month non-vertebral fracture rates that may be imbalance according to the actual treatment assignment.

2.2 Methods

2.2.1 Data Source

This study used the Medstat MarketScan Commercial Claims and Encounters (CCE) and Medicare Supplemental Database (Ann Arbor, MI). Data were available for 2005-2009 and partially for 2010. The MarketScan database captures the largest convenient sample of over 73 million unique patients. Since 1996, it has collected information mostly from large employers in the U.S.[71] This nationwide database contains over 500 million claim records per year from individuals with employer-sponsored health insurance. Information captured in the database includes patient demographics, detailed enrollment, inpatient services, physician encounters and pharmacy claims. Scientific studies based on this data source have been reported in more than 100 peer-reviewed articles.[71]

2.2.2 Study Design and Population

We conducted retrospective studies. **Figure 2-1** shows the sample selection strategy. We selected women, 50 years of age or older, who had ≥1 OP diagnosis between 2007 and 2009 (n=729,978). We further restricted the population to women who had continuous enrollment and ≥1 FRAX risk factors[73] but no diagnoses of Paget disease (ICD-9-CM code: 731.0) or malignancy (ICD-9-CM: 140-208) (n=128,859). We

then identified 116,359 women who initiated oral alendronate (10mg or 70mg) or risedronate (5mg or 35mg) or no OP treatment within 90 days after the index date (date of the first OP diagnosis). We excluded women who had any OP medications within 12 months before the index date (n=66,564). The final sample includes three groups: 1) women initiating an alendronate (n=3,717), 2) women initiating a risedronate (n=1,625) and 3) women with no OP treatment (n=37,948).

2.2.3 Measures

Outcome

The main outcome variable was an indicator of non-vertebral fracture (including hip, wrist/forearm and proximal humerus) at three months. It was identified during the first 3 months following the index date. We used diagnostic and procedure codes from claims to identify non-vertebral fractures based on approaches described by previous research.[38, 78]

Main Exploratory Variable

The main exploratory variable was an indicator of alendronate or risedronate. We identified alendronate or risedronate using national drug code (NDC).

Patient Characteristics

We determined patient demographic characteristics at the index date and other characteristics using claims from inpatient services, outpatient services and pharmacy

claims within 12 months before the index date. The characteristics included: 1) patient demographic (age); 2) history of non-vertebral fracture and diagnosis of osteoporosis; 3) co-morbidity measured by the Diagnostic Cost Group Hierarchical Condition Category (DCG/HCC) classification system (DxCG, Boston, MA);[88] 4) co-medications (drugs that may cause osteoporosis, treat/prevent osteoporosis and drugs associated with fracture); 5) health services utilization (hospitalization and screening mammogram); 6) geographic location of primary beneficiary's residence; and 7) types of health plans.

We measured patient's age in years. For patient history, a diagnosis of osteoporosis was defined as having a diagnostic code of 733.0x.[38] We defined history of non-vertebral fracture as having a diagnosis of hip fracture, wrist/forearm or proximal humerus within a year prior to the index date. We measured co-morbid condition using the DCG/HCC classification system. The DCG/HCC risk adjuster creates a single score for each person based on the presence of 189 medical conditions in the diagnosis fields of claims records. Despite its development for Medicare billing purpose, the DCG/HCC has been widely applied as a measure of confounding in studies of drug use.[89] We grouped concomitant medications based on their relationships with osteoporosis and fracture. Drugs that may cause osteoporosis included glucocorticoids,[90] H2 inhibitors, proton pump inhibitors (PPI)[91] and thyroid medications.[92] Drugs that treat or prevent osteoporosis included calcitonin, vitamin D, estrogen, selective estrogen receptor modulator (SERM) and parathyroid hormone.[15] Drugs that may be associated with fracture included psychotropic medications (benzodiazepine, selective serotonin reuptake inhibitor [SSRI], non-SSRI antipsychotic, anticonvulsant and hypnotics),[93] cardiovascular

medications (beta blocker and thiazide),[94, 95] and anti-inflammatory drugs (non-steroidal anti-inflammatory drug [NSAID] and cyclooxygenase 2 [COX2] inhibitor). Health services utilization variables included any hospitalization and any screening mammogram as proxy for health behavior. We categorized geographic location of primary beneficiary's residence into north central, northeast, south and west. Types of health plans included comprehensive plan, health maintenance organization (HMO), point of service (POS), and preferred provider organization (PPO).

Instrumental Variable

The instrumental variable, the date of generic alendronate availability, was defined as February 2008. We set it to 1 if after February 2008 and 0 otherwise.

2.2.4 Statistical Analysis

We performed the same analyses for comparing alendronate with no OP treatment and comparing alendronate with risedronate. We described analyses for one comparison (alendronate vs. risedronate) as an example. Our analyses emphasized on examining the two assumptions of a valid IV.

We described patient characteristics stratified by the two treatment groups (alendronate vs. risedronate) and by the two levels of the IV (before and after February 1, 2008). For the first assumption, we graphed the trend of the use of alendronate as compared with risedronate in the study sample over time. To examine the strength of the IV, we conducted a multivariate linear regression. We regressed the treat assignment on

the IV and other measured covariates including demographics, osteoporosis related factors, co-morbidity, medications, health services utilizations, region of residence and health plan types. We reported partial F statistic and partial R square for the IV.

We examined the second assumption based on approaches suggested by Brookhart et al and Newhouse and McClellan.[6, 81] We calculated standardized differences[82, 96] in patient characteristics between the two treatment groups and between the two levels of the IV to assess balance across measured confounders. A valid IV should have smaller standardized differences.

Furthermore, we calculated standardized difference in the 3-month non-vertebral fracture between the two treatment groups and the two levels of the IV. A valid IV should provide more balance of the 3-month non-vertebral fracture than the treatment assignment.

All analyses were conducted using STATA 10.0 (Stata Corp 2007, College Station, TX). The study received an exemption from the Institutional Review Board of University of Massachusetts Medical School.

2.3 Results

We identified a study cohort of 43,290 women. Among them 3,717 initiated an alendronate, 1,625 initiated a risedronate and 37,948 initiated no OP treatment (**Figure 2-1**). **Table 2-1** shows the characteristics of the cohort. The average age of the cohort was approximately 65 years. The mean co-morbidity score (DCG/HCC) was 0.86. Most

patients had comprehensive insurance or PPO and were located in the north central and the south.

Figure 2-2 provides information about the association between the IV and treatment assignment, when the comparator is no OP treatment. This figure shows that in the year before the availability of generic alendronate, only 10% of women who were at risk for osteoporotic fractures initiated alendronate therapy. After generic availability, this rate did not change. We conclude from this graph that the IV may not be strongly associated with the treatment choice (alendronate vs. no OP treatment).

Figure 2-3 illustrates the association between the IV and treatment assignment, when the comparator is risedronate. This figure shows that approximately 60% of women who were at risk for osteoporotic fractures initiated an alendronate in the year before the availability of generic alendronate. In contrast, this rate increased after generic alendronate availability with 92% of the women initiating an alendronate by the first quarter of 2009. We conclude from this graph that the IV may be strongly associated with the treatment choice (alendronate vs. risedronate).

Table 2-2 shows the strength of the IV in inducing variation of the treatment choice, as part of testing the first assumption. In the comparison of alendronate vs. no OP treatment, we found that IV explained only a modest amount of variation of the treatment assignment, although it was statistically significant. The partial F statistic was 5.24 and partial R square was 0.0001. In comparison, the IV explained more of the variation of treatment choice between receiving alendronate vs. risedronate (partial F

statistic = 301.99 and partial R square = 0.0538), and this was also statistically significant. We conclude from this table that the IV is a weak IV in the comparison of alendronate vs. no OP treatment while a strong one in the comparison of alendronate vs. risedronate.

Tables 2-3 and 2-4 demonstrate the ability of the IV to impose balance across measured characteristics of the study populations. **Table 2-3** shows the distribution of patient characteristics between women who initiated an alendronate and those with no OP treatment with and without the IV. Without the IV, we found that the two groups were quite different across most characteristics, and a simple comparison of treatment effects would be highly susceptible to bias. With the IV, we found that patient characteristics became more balanced before and after February 2008. For instance, compared to women without OP treatment, those who initiated an alendronate were older (mean age: 67 vs. 65), had a greater co-morbidity score (median DCG/HCC score 0.67 vs. 0.64) and had a higher history of osteoporotic fracture (7.65% vs. 11.43%). Women without OP treatment also had more medications and utilized more health services as compared to those with alendronate. Resorting the groups by the IV resulted in more balance of these characteristics, as evidence by the reductions in the standard differences. A reduction in imbalance can also be found in the history of non-vertebral fracture, one of the strongest predictors for fracture. We found 7.80% of women had a history of non-vertebral fracture before February 2008 and 8.20% after. In contrast, the proration with a history of non-vertebral fracture was lower in the group without OP treatment compared to the group with alendronate (11.43% vs. 7.65%).

Table 2-4 shows the distribution of patient characteristics between women who initiated an alendronate and who initiated a risedronate with and without the IV. We found that women with alendronate and those with risedronate were similar in characteristics with and without the IV. For instances, compared to patients initiating risedronate, those initiating alendronate were relatively younger (mean age: 67.20 vs. 67.30); had a higher proportion of fracture history (11.43% vs. 10.46); and had a lower co-morbidity score (median DCG/HCC score: 0.67 vs. 0.70). The medication utilizations were similar between the two groups. More women initiating a risedronate had a comprehensive health plan while more women initiating an alendronate had an HMO. For health services utilization, alendronate initiators had fewer hospitalizations (20.80% vs. 21.48%) and more screening mammograms (36.83% vs. 35.26 %). Resorting the groups by the IV did not result in more balance of these characteristics. The standardized differences in patient characteristics were even larger between the two levels of the IV than between treatment groups. We conclude from **Table 2-3** and **2-4** that the IV may provide better balance of patient characteristics in the comparison of alendronate vs. no OP treatment than in the comparison of alendronate vs. risedronate.

Table 2-5 also shows the indirect evidence for the validity of the IV according to the second assumption. This table shows the balance of the short term outcome, non-vertebral fracture at 3 months, with and without the IV. In the comparison of alendronate vs. no OP treatment, we found a 0.08% difference in the non-vertebral fracture at 3 months between the treatment and the control (alendronate vs. no OP treatment: 0.79% vs. 0.88%). Resorting the groups by the IV resulted in balance of the 3-month outcome

(before vs. after, February, 2008: 0.88% vs. 0.86%). The standard difference of the outcome was smaller with the IV than without the IV (IV vs. No IV: 0.06% vs. 0.24%). In the comparison of alendronate vs. risedronate, we found a 0.17% difference in the 3-month non-vertebral fracture (alendronate vs. risedronate: 0.79% vs. 0.96%). Resorting the groups by the IV provided more balance of the 3-month outcome (before vs. after, February, 2008: 0.83% vs. 0.86%). The standard difference of the outcome was smaller with the IV than without the IV (IV vs. no IV: 0.08% vs. 0.53%). We conclude from this table that the IV imposed more balance on 3-month non-vertebral fractures than the original treatment assignment.

2.4 Discussion

In this paper we introduced a new IV, the date of generic availability, and demonstrated how this IV performed when used to study treatment effectiveness with a "placebo" control and with an active control.

We reasoned that the date of generic availability would be associated with patient treatment choice (the first IV assumption) due to the lower price of the generic equivalent. We found empirical evidence supporting this argument in the literature. Furthermore, in our demonstration study, we found that the use of Fosamax and generic alendronate as compared with Actonel (risedronate) increased after the availability of generic alendronate, from approximately 60% among all women initiating an alendronate or risedronate in 2007 to approximately 90% in 2009. However, we did not find that overall use of alendronate increased among all women at risk for osteoporotic fractures.

This suggests that the IV may not be strongly associated with the treatment choice when the comparator is a "placebo" control.

In order to be a valid IV, the date of generic availability must also demonstrate the ability to balance measured and unmeasured confounders while not directly causing the outcome (the second IV assumption). This is not a directly verifiable assumption; however, we did provide both logical arguments and indirect empirical data to support this assumption. We further demonstrated that the IV could impose adequate balance of patient characteristics in comparisons of alendronate vs. no OP treatment and alendronate vs. risedronate although there was some residual imbalance in the comparison of alendronate vs. risedronate. Finally, we showed that the IV did not directly cause the outcome because the IV was not associated with the 3 month non-vertebral fracture. Comparing with the original treatment assignment, the IV provided more balance of the 3 month non-vertebral fracture. Therefore, the proposed IV satisfies the second assumption.

While we demonstrated the date of generic availability may be a valid IV for some comparative effectiveness studies it has limitations. First, this IV cannot be used in comparing two patent protected drugs. Second, the strength of this IV requires further examination, especially with other prescription drugs. Our own examination revealed that the IV appeared to be weak when the comparator was a "placebo" control (no OP treatment). A possible reason is that the prescribing pattern of OP treatment may not change because of the generic availability of alendronate. Without a strong variation in

the use of alendronate overtime, the first assumption of a valid IV is violated. In contrast, when we compared alendronate with risedronate, we found an increasing trend of using alendronate among women who initiated a study bisphosphonate (from 60% in 2007 to 90% in 2009). The high partial F statistic (F statistic = 301.99> 10) also supported this argument. This suggested that the date of generic alendronate availability did induce the variation in the use of alendronate among bisphosphonate users. A possible reason for this observation is that once a woman was prescribed a bisphosphonate treatment, she was more likely to receive an alendronate than a risedronate after generic alendronate availability.

Third, it appears that the IV, the date of generic availability, may perform best when there is strong evidence of confounding by indication; we can show that the IV not only balances observed patient characteristics but reduces the imbalance of these characteristics by original treatment groups. Moreover, it is unnecessary to apply the IV analysis without strong evidence of confounding by indication.[81] In our study comparing alendronate with no OP treatment, we expected a strong confounding by indication. Compared to women initiating an alendronate, women without OP treatment were younger, had less co-morbidity and history of fracture, and may have had healthier behaviors (unobserved). Whether a woman will receive an alendronate or no OP treatment may depend on these measured and unmeasured characteristics that are correlated with the outcome (non-vertebral fracture). We found that the IV could balance the observed patient characteristics which implied that it might also balance unmeasured characteristics. In contrast, in our example comparing alendronate with risedronate, we

did not find a reduced imbalance by the proposed IV because there was not strong evidence of confounding by indication.

Our study suggests that the date of generic availability may be a useful IV for studying the comparative effectiveness of prescription drugs. We also acknowledge that the proposed IV has limitations. Future research should evaluate whether the IV could induce the variation of treatment choice and examine the confounding by indication before applying this IV. Additionally further studies are warranted to provide evidence of the validity of the proposed IV in a variety of therapeutic areas.

Figure 2-1: Sample Selection Strategy

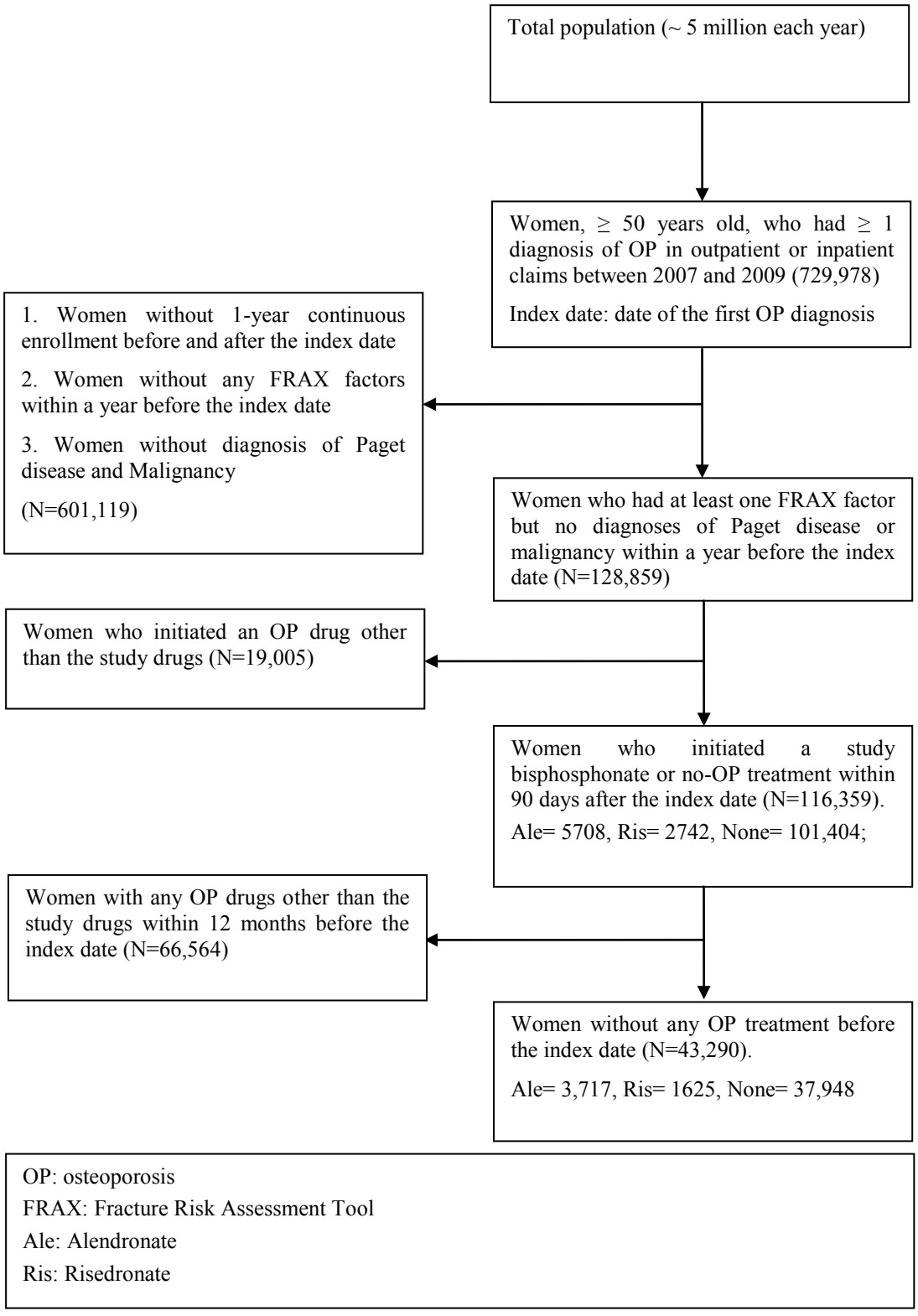


Figure 2-2: Choice of Alendronate vs. Non OP Treatment before and after Generic Availability of Alendronate

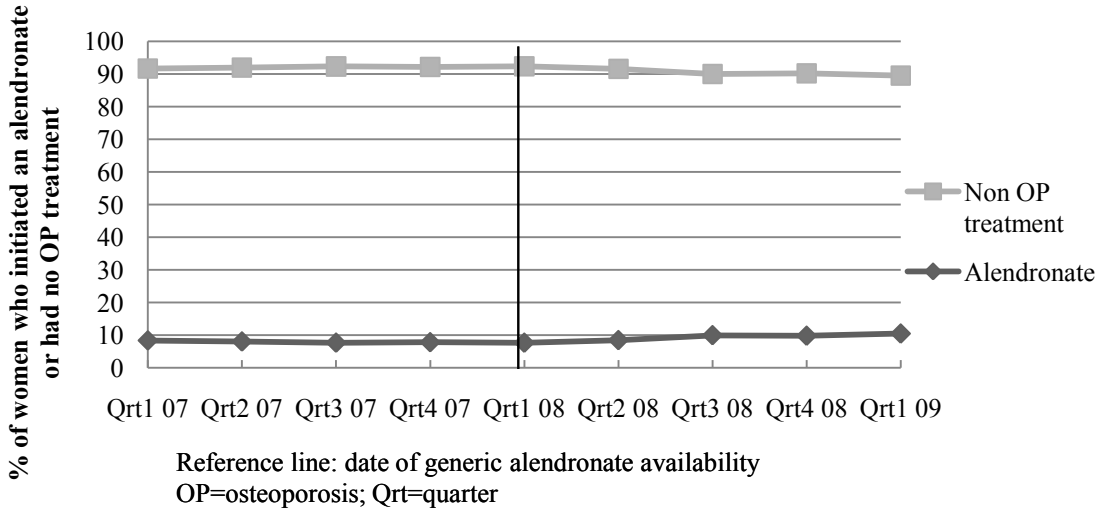
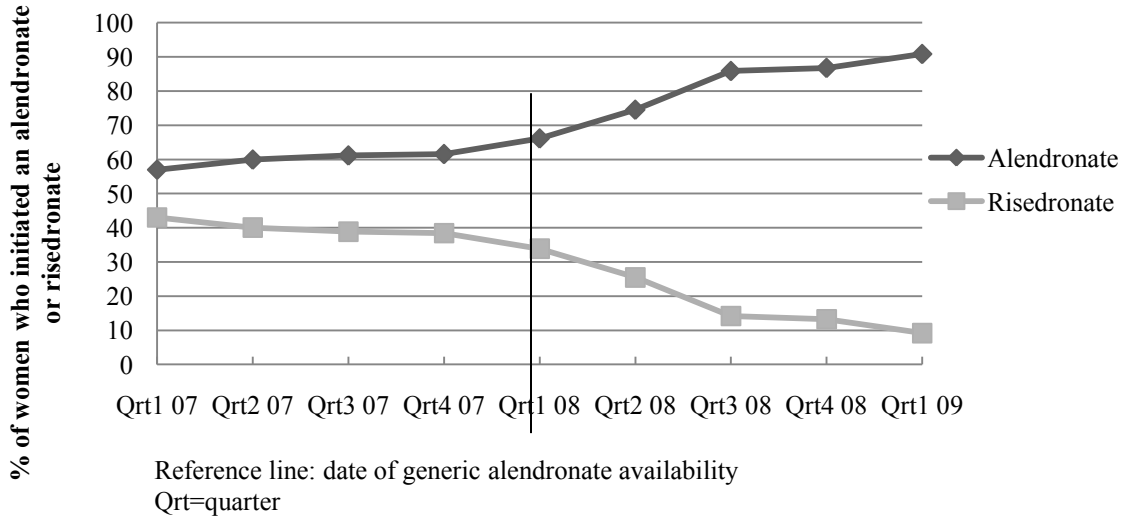


Figure 2-3: Choice of Alendronate vs. Risedronate before and after Generic Availability of Alendronate



Reference line: date of generic alendronate availability
Qrt=quarter

Table 2-1: Characteristics of the Study Population *

Total	37,948	
Age (mean, sd)	65.26	(11.34)
DCG/HCC		
Mean (Sd)	0.86	(0.75)
Median(25th – 75th percentile)	0.64	(0.38-1.07)
History of fracture	3499	(8.08)
Drugs that cause osteoporosis		
Glucocorticoid	30407	(70.24)
H2 inhibitor	2196	(5.07)
Proton pump inhibitor	14129	(32.64)
Thyroid drug	9314	(21.52)
Drugs associated with fracture		
Benzodiazepine	10838	(25.04)
SSRI/Non-SSRI	13427	(31.02)
Anticonvulsant	4060	(9.38)
Hypnotics	7825	(18.08)
B blocker	11644	(26.90)
Thiazide	4168	(9.63)
NSAIDS/Cox-2 inhibitor	13354	(30.85)
Health Plan type		
Comprehensive	16428	(37.95)
HMO	4906	(11.33)
POS	2922	(6.75)
PPO	19034	(43.97)
Geography		
North Central	14701	(33.96)
Northeast	5274	(12.18)
South	16074	(37.13)
West	7050	(16.29)
Health service utilization		
Hospitalization	8658	(20.00)
Mammogram	16009	(36.98)

* Data are given as number (percentage) unless otherwise indicated.

DCG/HCC= Diagnostic Cost Group Hierarchical Condition Category; SSRI=selective serotonin reuptake inhibitor; NSAIDS=non-steroidal anti-inflammatory drug; Cox-2=cyclooxygenase-2; HMO=Health Maintenance

Organization; POS=Point of Service; PPO=Preferred Provider Organization

Table 2-2: Strength of the IV Based on Generic Alendronate Availability in Comparative Effectiveness Research of Bisphosphonates*

	Partial F statistic	**Partial R square**	**P**
No osteoporosis treatment vs. alendronate	5.34	0.0001	<0.05
Alendronate vs. risedronate	301.99	0.0538	<0.01
* Adjusting for covariates including demographics, osteoporosis related factors, co-morbidity, medications, health services utilization, region of residence and health plan types.			

Table 2-3: Characteristics of Women Initiating an Alendronate or No Osteoporosis Treatment*

	Treatment assignment					Instrumental variable				
	No-OP treatment		Alendronate		Std. Dif	Before Feb, 2008		After Feb, 2008		Std. Dif
Total	37948		3717			22058		19607		
Age (mean, Sd)										
	65.00	(11.34)	67.20	(11.20)	-0.195	65.69	(11.44)	64.60	(11.21)	0.096
DCG/HCC										
Mean (Sd)	0.86	(0.75)	0.87	(0.73)	-0.014	0.87	(0.76)	0.84	(0.74)	0.040
History of fracture	2904	(7.65)	425	(11.43)	0.129	1721	(7.80)	1608	(8.20)	0.015
Drugs that cause osteoporosis										
Glucocorticoid	26689	(70.33)	2595	(69.81)	0.011	15194	(68.88)	14090	(71.86)	0.065
H2 inhibitor	1946	(5.13)	176	(4.74)	0.018	1045	(4.74)	1077	(5.49)	0.034
PPI	12499	(32.94)	1118	(30.08)	0.062	7120	(32.28)	6497	(33.14)	0.018
Thyroid drug	8269	(21.79)	723	(19.45)	0.058	4731	(21.45)	4261	(21.73)	0.007
Drugs associated with fracture										
Benzodiazepine	9526	(25.10)	898	(24.16)	0.022	5523	(25.04)	4901)	(25.00)	0.001
SSRI/Non-SSRI	11813	(31.13)	1124	(30.24)	0.019	6780	(30.74)	6157	(31.40)	0.014
Anticonvulsant	3577	(9.43)	336	(9.04)	0.013	1997	(9.05)	1916	(9.77)	0.025
Hypnotics	6898	(18.18)	616	(16.57)	0.043	4060	(18.41)	3454	(17.62)	0.021
B blocker	10257	(27.03)	988	(26.58)	0.010	5903	(26.76)	5342	(27.25)	0.011
Thiazide	3679	(9.69)	344	(9.25)	0.015	2110	(9.57)	1913	(9.76)	0.006
NSAIDS/Cox-2 inhibitor	11743	(30.94)	1120	(30.13)	0.018	6569	(29.78)	6294	(32.10)	0.050
Health Plan type										
Comprehensive	14948	(39.39)	996	(26.80)	0.270	8871	(40.22)	7073	(36.07)	0.086
HMO	4130	(10.88)	591	(15.90)	0.148	2195	(9.95)	2526	(12.88)	0.092
POS	2551	(6.72)	261	(7.02)	0.012	1359	(6.16)	1453	(7.41)	0.050
PPO	16319	(43.00)	1869	(50.28)	0.146	9633	(43.67)	8555	(43.63)	0.001
Geography										

North Central	12787	(33.70)	1360	(36.59)	0.061	7725	(35.02)	6422	(32.75)	0.048
Northeast	4721	(12.44)	365	(9.82)	0.083	2789	(12.64)	2297	(11.72)	0.028
South	14129	(37.23)	1294	(34.81)	0.050	8219	(37.26)	7204	(36.74)	0.011
West	6133	(16.16)	688	(18.51)	0.062	3250	(14.73)	3571	(18.21)	0.094
Health service utilization										
Hospitalization	7536	(19.86)	773	(20.80)	0.023	4451	(20.18)	3858	(19.68)	0.013
Mammogram	14067	(37.07)	1369	(36.83)	0.005	8077	(36.62)	7359	(37.53)	0.019

* Data are given as number (percentage) unless otherwise indicated.
DCG/HCC= Diagnostic Cost Group Hierarchical Condition Category; SSRI=selective serotonin reuptake inhibitor; NSAIDS=non-steroidal anti-inflammatory drug; Cox-2=cyclooxygenase-2; HMO=Health Maintenance Organization; POS=Point of Service; PPO=Preferred Provider Organization

Table 2-4: Characteristics of Women Initiating an Alendronate or Risedronate *

	Treatment assignment					Instrumental variable				
	Risedronate		Alendronate		Std. Dif	Before Feb, 2008		After Feb, 2008		Std. Dif
Total	1625		3717			3126		2216		
Age (mean, sd)	67.30	(10.97)	67.20	(11.20)	0.009	67.4	(11.06)	66.97	(11.21)	0.039
DCG/HCC										
Mean (SD)	0.89	(0.75)	0.87	(0.73)	0.027	0.89	(0.76)	0.85	(0.70)	0.055
History of fracture	170	(10.46)	425	(11.43)	0.031	345	(11.04)	250	(11.28)	0.008
Drug that cause osteoporosis										
Glucocorticoid	1123	(69.11)	2595	(69.81)	0.015	2117	(67.72)	1601	(72.25)	0.099
H2 inhibitor	74	(4.55)	176	(4.74)	0.009	139	(4.45)	111	(5.01)	0.026
Proton pump inhibitor	512	(31.51)	1118	(30.08)	0.031	975	(31.19)	655	(29.56)	0.035
Thyroid drug	322	(19.82)	723	(19.45)	0.009	592	(18.94)	453	(20.44)	0.038
Drugs associated with fracture						0.031				
Benzodiazepine	414	(25.48)	898	(24.16)	0.031	780	(24.95)	532	(24.01)	0.022
SSRI/Non-SSRI	490	(30.15)	1124	(30.24)	0.002	957	(30.61)	657	(29.65)	0.021
Anticonvulsant	147	(9.05)	336	(9.04)	0.000	279	(8.93)	204	(9.21)	0.010
Hypnotics	311	(19.14)	616	(16.57)	0.067	547	(17.50)	380	(17.15)	0.009
B blocker	399	(24.55)	988	(26.58)	0.047	833	(26.65)	554	(25.00)	0.038
Thiazide	145	(8.92)	344	(9.25)	0.011	288	(9.21)	201	(9.07)	0.005
NSAIDS/Cox-2 inhibitor	491	(30.22)	1120	(30.13)	0.002	917	(29.33)	694	(31.32)	0.043
Health Plan type										
Comprehensive	484	(29.78)	996	(26.80)	0.066	879	(28.12)	601	(27.12)	0.022
HMO	185	(11.38)	591	(15.90)	0.132	388	(12.41)	388	(17.51)	0.143
POS	110	(6.77)	261	(7.02)	0.010	224	(7.17)	147	(6.63)	0.021
PPO	846	(52.06)	1869	(50.28)	0.036	1635	(52.30)	1080	(48.74)	0.071

Geography										
North Central	554	(34.09)	1360	(36.59)	0.052	1116	(35.70)	798	(36.01)	0.006
Northeast	188	(11.57)	365	(9.82)	0.057	352	(11.26)	201	(9.07)	0.073
South	651	(40.06)	1294	(34.81)	0.109	1173	(37.52)	772	(34.84)	0.056
West	229	(14.09)	688	(18.51)	0.120	478	(15.29)	439	(19.81)	0.119
Health service utilization										
Hospitalization	349	(21.48)	773	(20.80)	0.017	687	(21.98)	435	(19.63)	0.058
Mammogram	573	(35.26)	1369	(36.83)	0.033	1150	(36.79)	792	(35.74)	0.022

* Data are given as number (percentage) unless otherwise indicated.
DCG/HCC= Diagnostic Cost Group Hierarchical Condition Category; SSRI=selective serotonin reuptake inhibitor; NSAIDS=non-steroidal anti-inflammatory drug; Cox-2=cyclooxygenase-2; HMO=Health Maintenance Organization; POS=Point of Service; PPO=Preferred Provider Organization

Table 2-5: Non-vertebral Fracture at 3 Months Stratified by Different Treatment Groups and the Two Levels of the IV among Women at Risk for Osteoporotic Fracture*

	No OP treatment vs. Alendronate					
3-month non-vertebral fracture (%)	**Original treatment assignment**			**IV**		
	No OP treatment	Alendronate	Std. dif	Before Feb, 2008	After Feb, 2008	Std. dif
	0.88	0.79	0.24	0.88	0.86	0.06
	Alendronate vs. Risedronate					
	Original treatment assignment			**IV**		
	Alendronate	Risedronate	Std. dif	Before Feb, 2008	After Feb, 2008	Std. dif
	0.79	0.96	0.53	0.83	0.86	0.08

* All comparison are not statistically significant (P>0.05)

Std. dif = standard difference

3 CHAPTER III: COMPARATIVE EFFECTIVENESS OF ALENDRONATE AND RISEDRONATE ON NON-VERTEBRAL FRACTURES: AN INSTRUMENTAL VARIABLES ANALYSIS

3.1 Introduction

Osteoporosis is a skeletal disorder leading to increased risk of fractures in older people.[8] About 54% women, age 50 or older, will have osteoporosis-related fractures during the course of their lives.[11] Bisphosphonates are the leading pharmacologic treatment for osteoporosis and prevention of osteoporotic fractures.[4] Among all bisphosphonates, alendronate and risedronate are the most commonly prescribed agents[4, 38]. While randomized control trials (RCTs) have shown that both agents reduce the risk of non-vertebral fractures, evidence from head-to-head trials comparing alendronate and risedronate is lacking due to substantial logistic and financial burdens.[37] Nevertheless, the comparative effectiveness of the two agents is important because alendronate (brand name: Fosamax) is available in a generic form and risedronate (brand name: Actonel) is not.

Observational studies can provide meaningful information on the comparative effectiveness of the two medications on the risk of non-vertebral fractures. Watts et al.[36] and Silverman et al.[3] found significant risk reduction for risedronate vs. alendronate in women, 65 years of age or older, at 6, 12 and 24 months (HR ranged from 0.41 to 0.82). However, Cutis et al.[37] and Cadarette et al.[38] showed the difference in the risk of non-vertebral fracture between older women (65 years or older) on risedronate and alendronate was small and not statistically significant (HR ranged from 0.96 to 1.07). Despite using similar observational study designs, statistical analyses and confounding adjustments, inconsistent results appeared in these studies. One possible explanation for

such an inconsistency is that observational studies may suffer from confounding bias from unmeasured variables.[3, 37] Studies applying methods to adjust for potential unmeasured confounding can provide further information on the comparative effectiveness of these medications[38].

Instrumental variables (IV) analysis, recently introduced to medical research, is a methodological approach used to reduce bias due to unmeasured confounding.[6] It has been demonstrated to provide estimates of effect comparable to those from RCTs.[48] Therefore, we conducted a head-to-head comparison between alendronate and risedronate on the risk of non-vertebral fractures using observational data and an IV analysis. We hypothesize that alendronate has a comparable effect to risedronate on the risk of one-year non-vertebral fracture in women, 50 years of age or older. We propose a new IV based on generic utilization of alendronate which may be used for comparative effectiveness research of other prescription drugs.

3.2 Methods

3.2.1 Data Source

This study used the Medstat MarketScan Commercial Claims and Encounters (CCE) and Medicare Supplemental Database (Ann Arbor, MI). Data were available for 2005-2009 and partial for 2010. The MarketScan database captures the largest convenient sample of over 107 million unique patients. Since 1996, it has collected information mostly from large employers in the U.S.[71, 72] This nationwide database

contains over 500 million claim records per year from individuals with employer-sponsored health insurance. Information captured in the database includes patient demographics, detailed enrollment, inpatient services, physician encounters and pharmacy claims. Scientific studies based on this data source have been reported in more than 75 peer-reviewed articles[71].

3.2.2 Study Design and Population

We conducted a retrospective cohort study and adopted a new user design.[75] **Figure 3-1** shows the sample selection strategy. We selected women, 50 years of age or older, who had enrollment information between 2007 and 2009 (N=8,034,624). We then identified women who initiated an oral alendronate (10mg or 70mg) or risedronate (5mg or 35mg) during the time period and had continuous enrollment before and after the index date ─ date of initiation of an alendronate or risedronate (N=360,857). Individuals were excluded if: 1) they had a bisphosphonate within 12 months before the index date (N=249,048); and 2) they had a diagnosis of Paget's disease (ICD-9-CM code: 731.0) or malignant neoplasm (ICD-9-CM: 140-208) within one year before the index date (N=11,496). The final sample included 100,313 women, among whom 71,034 initiated an alendronate and 29,279 risedronate.

3.2.3 Measures

Outcomes

The main outcome variable was an indicator of non-vertebral fracture (including hip, wrist/forearm and proximal humerus). It was identified during the first 6 and 12 months following the index date. We used diagnostic and procedure codes from claims to identify non-vertebral fractures based on approaches described by previous research[38, 78] (**appendix I** shows diagnostic and procedure codes).

Main Exploratory Variable

The main exploratory variable was an indicator of alendronate (10mg or 70mg) or risedronate (5mg or 35mg). We identified alendronate or risedronate using national drug code (NDC) and **appendix II** shows the codes.

Covariates

We determined patient demographic characteristics at the index date and other characteristics using claims from inpatient services, outpatient services and pharmacy claims within 12 months before the index date (**appendix III**). The characteristics included: 1) patient demographic (age); 2) history of non-vertebral fracture and diagnosis of osteoporosis; 3) co-morbidity measured by the Diagnostic Cost Group Hierarchical Condition Category (DCG/HCC) classification system (DxCG, Boston, MA)[88]; 4) co-medications (drugs that may cause osteoporosis, treat/prevent osteoporosis and drugs associated with fracture); 5) health services utilization (hospitalization and screening mammogram); 6) geographic location of primary beneficiary's residence; and 7) types of health plans.

We measured patient's age in years. For patient history, a diagnosis of osteoporosis was defined as having a diagnostic code of 733.0x.[38] We defined history of non-vertebral fracture as having a diagnosis of hip fracture, wrist/forearm or proximal humerus within a year prior to the index date. We measured co-morbid condition using the DCG/HCC classification system. The DCG/HCC risk adjuster creates a single score for each person based on the presence of 189 medical conditions in the diagnosis fields of claims records. Despite its development for Medicare billing purpose, the DCG/HCC has been widely applied as a measure of confounding in studies of drug use.[89] We grouped concomitant medications based on their relationships with osteoporosis and fracture. Drugs that may cause osteoporosis included glucocorticoids[90], H2 inhibitors, proton pump inhibitors (PPI)[91] and thyroid medications.[92] Drugs that treat or prevent osteoporosis included calcitonin, vitamin D, estrogen, selective estrogen receptor modulator (SERM) and parathyroid hormone.[15] Drugs that may be associated with fracture included psychotropic medications (benzodiazepine, selective serotonin reuptake inhibitor [SSRI], non-SSRI antipsychotic, anticonvulsant and hypnotics)[93], cardiovascular medications (beta blocker and thiazide)[94, 95], and anti-inflammatory drugs (non-steroidal anti-inflammatory drug [NSAID] and cyclooxygenase 2 [COX2] inhibitor). Health services utilization variables included any hospitalization and any screening mammogram as proxy for health behavior. We categorized geographic location of primary beneficiary's residence into north central, northeast, south and west. Types of health plans included comprehensive plan, health maintenance organization (HMO), point of

service (POS), and preferred provider organization (PPO). A detailed list of covariates can be found in the **appendix III**.

Instrumental Variables

We adopted an instrumental variable approach to address confounding from unmeasured variables. The instrumental variable we used was based on calendar time, specifically, the date of generic alendronate availability (February 1, 2008).

An instrument variable is valid if it meets two key assumptions: 1) the IV should be associated with the treatment assignment and 2) the IV has no relationship with measured and unmeasured confounders and does not directly cause the outcome[6, 44]. Theoretically, the date of generic alendronate availability satisfies the two key assumptions. First, the use of a drug will increase after its patent protection expires partially because of the price drop.[97] Generic alendronate has been on the market since February 1, 2008, while the patent of Actonel (brand name for risedronate) has not expired yet. Therefore, the use of alendronate in comparison to risedronate would increase after alendronate went generic. Second, a historical date is independent of the characteristics of a population because they do not change dramatically over a short time period. In addition, a historical date does not affect patient outcome. Therefore the date of generic alendronate availability meets the second assumption.

3.2.4 Statistical Analysis

Descriptive Statistics

We presented means and standard deviations for continuous variables, and frequencies and proportions for discrete variables. We described the distribution of patient characteristics by the original treatment assignment (alendronate and risedronate) and then by two levels of the IV (before and after February 1, 2008). We graphed the trend of the use of alendronate in the study sample over time (**Figure 3-2**).

Conventional univariate and multivariate analyses

We examined the crude association between study bisphosphonates and non-vertebral fracture outcome at 6 and 12 months using simple linear regressions. In the multiple linear regressions, we assessed the association adjusting for variables described in the covariates section. We reported risk difference (RD) from the linear regressions. We chose linear regression because it estimated RDs which were comparable to IV estimates and have been applied in previous research.[45, 98]

Instrumental Variables (IV) Analysis

We used a 2-stage least square (2SLS) regression for the IV analysis and RD was reported per 100 patients. We built two simultaneous equations (equation 1 and 2). In the first stage (equation 1), we regressed the treatment variable on the IV and other measured covariates. In equation 1, E[T|IV] indicates the expected value of the treatment assignment for the i^{th} patient given the IV after controlling for measured covariates. T equals 1 when the patient receives an alendronate and 0 otherwise. IV is the date of generic alendronate availability. It equals 1 when the date is after February 1, 2008 and 0

otherwise. X is a vector of measured covariates. $\hat{\alpha}_1$ estimates the increase of the probability of initiating an alendronate after it turns generic adjusting for other measured covariates.

In the second stage (equation 2), we regressed the outcome on the expected values of treatment assignment (E[T|IV]) obtained from the first stage and other measured covariates. Y_i represents the outcome of the ith patient, an indicator of non-vertebral fracture. It equals 1 when a patient has at least one non-vertebral fracture and 0 otherwise. $\hat{\beta}_1$ is the IV estimator.

Equation (1)

$$E[T \mid IV] = \Pr(T_i = 1 \mid IV_{i,} X_i) = \alpha_0 + \alpha_1 IV + \sum_{j=2}^{m} \alpha_j X_{ji}$$

Equation (2)

$$E[Y \mid IV] = \Pr(Y_i = 1 \mid \Pr(T_i = 1 \mid IV_i, X_i), X_i) = \beta_0 + \beta_1 \Pr(T_i = 1 \mid IV_i, X_i) + \sum_{j=2}^{m} \beta_j X_{ji}$$

All analyses were performed using STATA 10. We used IVREG2 for the IV analysis. The study was approved by the Institutional Review Board of the University of Massachusetts Medical School.

3.3 Results

We identified 100,313 women, among whom 71,034 initiated an alendronate and 29,279 risedronate. Among women instantiating an alendronate, 2.04 % (n=1449) and 2.89% (n=2,053) had a non-vertebral fracture in the following 6 and 12 months respectively, while they were 1.85% (n=542) and 2.69% (n=789) for women initiating a risedronate in the following 6 and 12 months respectively. We also stratified the sample by the date of the generic availability of alendronate. There were 61,757 women who initiated a study bisphosphonate before February 1, 2008 and 38,556 after. Among women initiating a bisphosphonate before February 1, 2008, 1.87% (n=1,156) and 2.69% (n=1,661) had a non-vertebral fracture at 6 and 12 months respectively. Among women initiating a bisphosphonate after February 1, 2008, 2.17% (n=835) and 3.06% (n=1,181) had a non-vertebral fracture at 6 and 12 months respectively **(Appendix IV**).

Table 3-1 shows the distribution of patient characteristics stratified by the original treatment assignment (alendronate or risedronate). In general, differences in patient characteristics between the two treatment groups are relatively small, although most p values are less than 0.05 due to large sample size. Compared to patients taking risedronate, those taking alendronate were relatively older (mean age: 65 vs. 64); had a higher proportion of fracture history (3.68% vs. 3.30) and diagnosis of osteoporosis (33.63% vs. 32.00%). Patients taking alendronate also received relatively more medications. However, the distribution of vitamin D is substantially imbalanced between the two groups (22.99% vs. 3.07%). For health services utilization, alendronate users had more hospitalizations (12.27% vs. 11.75%) and fewer screening mammograms (52.68% vs. 55.60%). More patients taking alendronate lived in West, while more risedronate

users lived in the South. Compared to risedronate users, alendronate users had a relatively higher proportion of enrollment in HMOs and a lower proportion of enrollment in PPOs.

Table 3-2 shows the distribution of patient characteristics before and after the availability of generic alendronate, February 1, 2008. In general, differences in patient characteristics between the two levels of the IV are also relatively small, although most p values are less than 0.05 due to large sample size. The IV provides more balance in some characteristics such as vitamin D (19.00% vs. 14.25%), parathyroid hormone (1.20% vs. 1.19%), calcitonin (1.56% vs. 1.61%) and screening mammogram (54.20% vs. 52.47%). Some characteristics are less balanced between the two levels of the IV such as thyroid drug (18.04% vs. 19.46%), benzodiazepine (16.72% vs.18.57%) and hypnotics (12.10% vs. 13.01%).

Figure 3-2 shows the choice of alendronate or risedronate before and after the availability of generic alendronate. We found that among all patients in the sample, approximately 60% initiated alendronate in January 2007 and the use of alendronate did not change before February 1, 2008. After generic alendronate became available on February 1, 2008, the use of this medication increased dramatically with 92% of the sample initiating alendronate by May 2009. In contrast, the use of risedronate did not change before February 1, 2008; however, it decreased after.

Table 3-3 shows the unadjusted and adjusted association between alendronate in relative to risedronate on the risk of non-vertebral fractures using conventional simple and multiple linear regressions. At 6 months, compared to women with risedronate, those

with alendronate had higher risk of non-vertebral fracture (unadjusted RD, 0.19 per 100 women, confidence interval [CI], -0.00-0.38 per 100 women). After adjusting for patient characteristics, the RD decreased (adjusted RD, 0.12 per 100 women, 95%CI -0.06-0.30 per 100 women). At 12 months, we found that women taking alendronate had higher but not significant risk of non-vertebral fracture compared with women taking risedronate (unadjusted RD, 0.20 per 100 women; 95%CI, -0.03-0.42 per 100 women). Adjusting for patient characteristics did not change the association (adjusted RD, 0.10 per 100 women; 95% CI, -0.12-0.31per 100 women). In the IV analysis, the first stage partial R square was 0.04 and F statistic was 3953.40 indicating a strong IV. The IV analysis showed similar findings (**Table 3-3**). Using risedronate as the reference, alendronate showed a subtle but not significant increase in the risk of non-vertebral fracture at 6 months (RD, 0.17 per 100 women; 95%CI, -0.76-1.10 per 100 women). The association did not change at 12 months (RD, 0.27 per 100 women; 95%CI, -0.86-1.14 per100 women).

3.4 Discussion

We compared the effect of alendronate with risedronate on the risk of one-year non-vertebral fractures in women, 50 years or older, using claims data from multiple health plans across the US. Our conventional analysis showed a comparable effect of alendronate vs. risedronate on the risk of non-vertebral fractures (at 6 months: adjusted RD = 0.12 per 100 women, 95%CI [-0.06-0.30]; at 12 months: adjusted RD = 0.10 per 100 women, 95%CI [-0.12-0.31]). The results of the IV analysis were consistent with those from the conventional analysis (at 6 months: RD=0.17 per 100 women, 95%CI [-

0.76-1.10]; at 12 months: RD=0.27 per 100 women, 95%CI [-0.86-1.14]. As an ad hoc analysis we excluded women who had a history of non-vertebral fracture in the analysis because patients with a history of fracture may react differently to osteoporosis treatment for patients without a history of fracture. We found similar results; therefore we reported the analysis include the fracture history. Our results are consistent with the two latest observational studies by Curtis et al.[37] and Caderette et al.[38].

However, our results differ from findings of two earlier studies by Watts et al.[36] and Silverman et al.[3] Methodological differences in study design and analysis may partially explain such discordance. First, we limited our study to alendronate and risedronate approved for osteoporosis treatment purpose, while the others included doses for prevention. Second, we defined our patient characteristics using data at baseline and one year historical period, while Watts et al. assessed patient characteristics at baseline and Silverman et al. at baseline and 6-month historical period. Finally we included women, 50 years of age or older, while the others included women who were at least 65 years of age. The inclusion of younger and possibly healthier women increased the generalizability of our results. It might, however, affect our results towards null. As a post hoc analysis, we repeated our analysis on women, 65 years of age or older and found similar estimates.

One important improvement of our study compared with previous studies is that we applied an econometric method to account for unmeasured confounding that had not been fully addressed by previous studies. IV analysis has gained popularity in

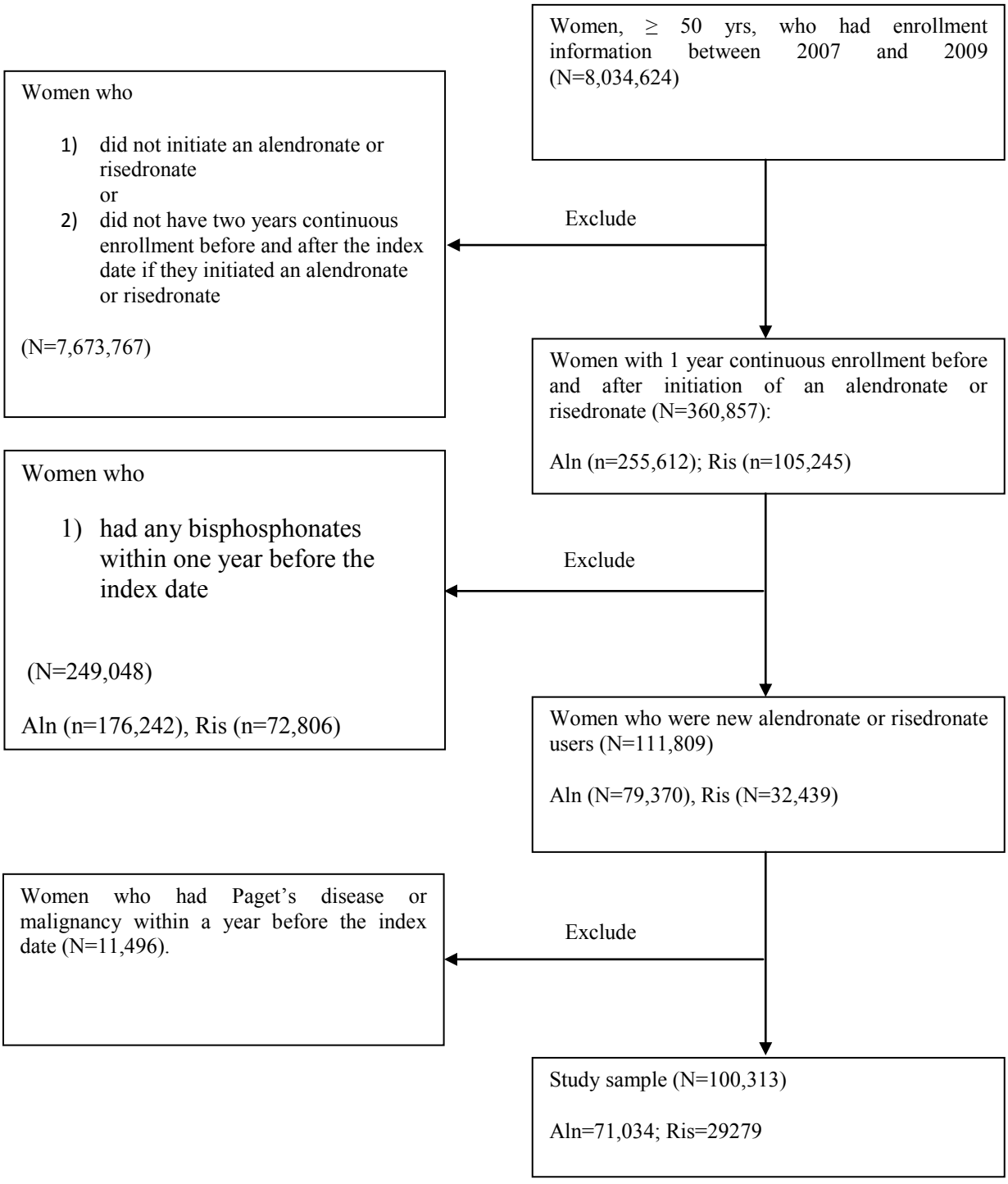
comparative effectiveness research of prescription medications[46]. A valid IV needs to meet two key assumptions: 1) the IV is associated with the treatment assignment; 2) it is independent of measured and unmeasured confounders and has not direct effect on the outcome. Our IV, the date of generic availability of alendronate, is valid. First, we reasoned that cost reduction of Fosamax (brand name of alendronate) after the generic form was on the market might be a factor affecting decision of initiating an alendronate or a risedronate. We provided empirical evidence showing that the probability of initiating an alendronate increased significantly after its generic availability (**Figure 3-2**). Furthermore, such an increase was attributable to the generic utilization. More than 90% of alendronate initiated by May 2009 were in generic form (data not shown). Second, it is impossible to directly verify the second assumption. Brookhart[81] suggested that the IV should provide balance for measured confounders. We reported that patient characteristics were quite evenly distributed between the two levels of the IV. We did not see a substantial reduction in imbalance of patient characteristics by the IV because patient characteristics were already evenly distributed between original treatment assignments. However, we reported the IV analysis because it provided further adjustment for unmeasured confounders. Finally, theoretical foundation of the IV proposed in this paper may be used for comparative effectiveness research of mediation other than alendronate. It is particularly usefully for medications that have strong confounding by indication

This study is also subject to limitations. First, we identified non-vertebral fracture outcome using claims data. Potential misclassification was possible. However, our

approach of identifying non-vertebral fractures has been applied by other research and study has shown that using claims data to identify fracture outcomes will achieve 90% sensitivity if medical records are the reference standard[77]. Second, the study was limited to employed women who had employer-sponsored insurance. The result is not generalizable to unemployed or uninsured women. Third, although patient characteristics were evenly distributed between two levels of the IV, the IV did not show a significant reduction in imbalance of these characteristics. This might be due to the inclusion of insured women in this study. A study including samples from uninsured women might improve the IV analysis because they may be more sensitive to price of a medication and have different characteristics from the insured. Finally, our results should be explained in the context of observational study. A randomized trial is warranted to provide better evidence.

In conclusion, the reduction in the risk of one-year non-vertebral fractures is comparable between alendronate and risedronate in women 50 years of age or older. The IV based on the time of generic form availability may be useful for comparative effectiveness research of prescription drugs in general.

Figure 3-1: Sample Selection Strategy *



***Aln=Alendronate, Ris =Risedronate**

Table 3-1: Characteristics of Women Initiating an Alendronate or Risedronate Between 2007 and 2009*

	Alendronate		Risedronate	
N of patients	71034		29279	
Demographics				
Age	65	(10.77)	64	(10.76)
History				
History of non-vertebral fracture	2613	(3.68)	966	(3.30)
Osteoporosis	23889	(33.63)	9370	(32.00)
Co-morbidity (DCG/HCC)	0.6	(0.51)	0.6	(0.54)
Drug that cause osteoporosis				
Glucocorticoid	18000	(25.34)	7274	(24.84)
H2 inhibitor	2894	(4.07)	983	(3.36)
Proton pump inhibitor	15673	(22.06)	6724	(22.97)
Thyroid drug	13187	(18.56)	5459	(18.64)
Drugs that treat/prevent osteoporosis				
Vitamin D	16332	(22.99)	898	(3.07)
Estrogen	9289	(13.08)	4144	(14.15)
SERMS	2847	(4.01)	1206	(4.12)
Parathyroid hormone	805	(1.13)	395	(1.35)
Calcitonin	1054	(1.48)	532	(1.82)
Drugs associated with fracture				
Benzodiazepine	12442	(17.52)	5041	(17.22)
SSRI/Non-SSRI	19322	(27.20)	7814	(26.69)
Anticonvulsant	5052	(7.11)	1940	(6.63)
Hypnotics	8749	(12.32)	3736	(12.76)
B blocker	15336	(21.59)	6002	(20.50)
Thiazide	6618	(9.32)	2287	(7.81)
NSAIDS/Cox-2 inhibitor	18256	(25.70)	7001	(23.91)
Health service utilization				
Hospitalization	8714	(12.27)	3439	(11.75)
Mammogram	37422	(52.68)	16279	(55.60)
Geography¶				
North Central	22619	(31.84)	9832	(33.58)
Northeast	6213	(8.75)	2526	(8.63)
South	25799	(36.32)	12500	(42.69)
West	16219	(22.83)	4352	(14.86)
Health Plan type¶				

Comprehensive	14034 (19.76)	5976 (20.41)
HMO	13340 (18.78)	3660 (12.50)
POS	5806 (8.17)	2441 (8.34)
PPO	36857 (51.89)	16765 (57.26)

* Data are given as number (percentage) unless otherwise indicated.

¶ Numbers in cells are proportion and 95%CI

DCG/HCC= Diagnostic Cost Group Hierarchical Condition Category; SSRI=selective serotonin reuptake inhibitor; NSAIDS=non-steroidal anti-inflammatory drug; Cox-2=cyclooxygenase-2; HMO=Health Maintenance Organization; POS=Point of Service; PPO=Preferred Provider Organization

Table 3-2: Characteristics of women before and after generic availability of alendronate, February 1,2008 *

	Before Feb, 2008		After Feb, 2008	
N of patients	61757		38556	
Demographics				
Age (mean, sd)	64	(10.67)	65	(10.89)
History of non-vertebral fracture	2065	(3.34)	1514	(3.93)
Osteoporosis	20014	(32.41)	13245	(34.35)
Co-morbidity (DCG/HCC) (mean, sd)	0.59	(0.53)	0.61	(0.52)
Drug that cause osteoporosis				
Glucocorticoid	14942	(24.19)	10332	(26.80)
H2 inhibitor	2038	(3.30)	1839	(4.77)
Proton pump inhibitor	13445	(21.77)	8952	(23.22)
Thyroid drug	11144	(18.04)	7502	(19.46)
Drugs that treat/prevent osteoporosis				
Vitamin D	11736	(19.00)	5494	(14.25)
Estrogen	8552	(13.85)	4881	(12.66)
SERMS	2470	(4.00)	1583	(4.11)
Parathyroid hormone	743	(1.20)	457	(1.19)
Calcitonin	964	(1.56)	622	(1.61)
Drugs associated with fracture				
Benzodiazepine	10323	(16.72)	7160	(18.57)
SSRI/Non-SSRI	16337	(26.45)	10799	(28.01)
Anticonvulsant	4051	(6.56)	2941	(7.63)
Hypnotics	7470	(12.10)	5015	(13.01)
B blocker	12540	(20.31)	8798	(22.82)
Thiazide	5222	(8.46)	3683	(9.55)
NSAIDS/Cox-2 inhibitor	14921	(24.16)	10336	(26.81)
Health service utilization				
Hospitalization	7244	(11.73)	4909	(12.73)
Mammogram	33470	(54.20)	20231	(52.47)
Geography¶				
North Central	20799	(33.68)	11652	(30.22)
Northeast	5388	(8.72)	3351	(8.69)
South	23876	(38.66)	14423	(37.41)
West	11541	(18.69)	9030	(23.42)
Health Plan type¶				
Comprehensive	12292	(19.90)	7718	(20.02)

HMO	9009 (14.59)	7991 (20.73)
POS	4735 (7.67)	3512 (9.11)
PPO	35129 (56.88)	18493 (47.96)

* Data are given as number (percentage) unless otherwise indicated.
¶ Numbers do not add to 100% because of missing data
DCG/HCC= Diagnostic Cost Group Hierarchical Condition Category; SSRI=selective serotonin reuptake inhibitor; NSAIDS=non-steroidal anti-inflammatory drug; Cox-2=cyclooxygenase-2; HMO=Health Maintenance Organization; POS=Point of Service; PPO=Preferred Provider Organization

Figure 3-2: Choice of Alendronate or Risedronate before and after Generic Alendronate Availability

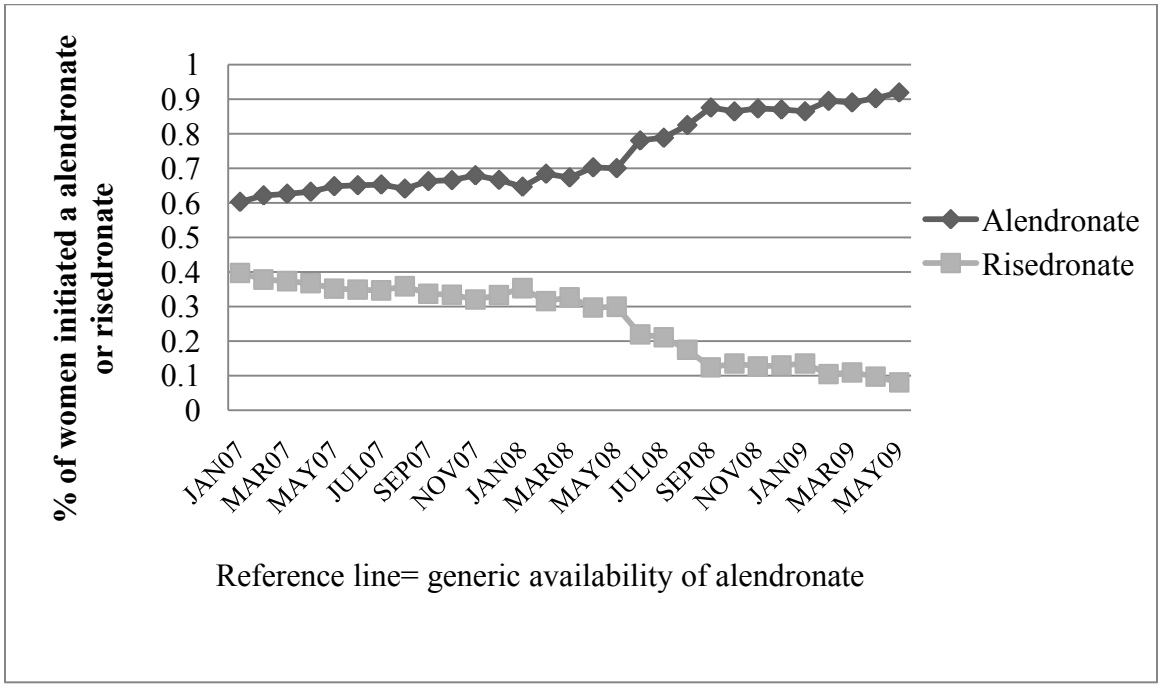


Table 3-3: Comparing the Effect of Alendronate vs. Risedronate on the Risk of Non-vertebral Fractures in 12 Months*

	6 months		12 months	
	RD	**95%CI**	**RD**	**95%CI**
Unadjusted (cases/100 patients)	0.19	-0.00-0.38	0.20	-0.03-0.42
Adjusted (cases/100 patients) ¶	0.12	-0.06-0.30	0.10	-0.12-0.31
IV estimator (cases/100 patients) ¶	0.17	-0.76-1.10	0.27	-0.86-1.14

* Reference group = risedronate; RD=risk difference; CI=confidence interval; IV=instrumental variables

¶Adjusting for covariates including demographic characteristics, osteoporosis related factors, co-morbidity, concomitant medications, health services utilization region of residence and health plan types.

4 CHAPTER IV: COMPARATIVE EFFECTIVENESS OF ALENDRONATE AND RISEDRONATE ON THE RISK OF NON-VERTEBRAL FRACTURES: USING TWO VALID INSTRUMENTAL VARIABLES

4.1 Introduction

In February of 2008, the block buster prescription drug Fosamax (alendronate) became the first bisphosphonate to be available as a generic drug, which substantially reduces its cost (looking for data). Bisphosphonates are a class of drugs that inhibitor bone resorption and are commonly prescribed for treatment and prevention of osteoporosis (OP) in postmenopausal women.[1, 2, 15] However, despite the lower costs of generics, brand name prescribing of bisphosphonates still occurs -- as of the first quarter of 2009, among patients initiating a bisphosphonate, approximately 8% was for Actonel (risedronate) despite unclear evidence of any efficacy superiority (as discussed in **Aim 2**).

There are no randomized controlled trials (RCTs) assessing the comparative effectiveness of the two bisphosphonates on the risk of non-vertebral fractures in older women. Head-to-head trails using intermediate endpoints of bone mineral density (BMD) have shown that alendronate has slightly advantage over risedronate.[15] Therefore, evidence of the comparative effectiveness of alendronate vs. risedronate on the risk of non-vertebral fractures may provide important information for physicians and patients to choose a cost-effective strategy to treat osteoporosis and prevent osteoporotic fractures. However, existing observational studies have shown inconsistent results.[3, 36-38] Two earlier studies showed that risedronate reduced more of the risk of one-year non-vertebral fractures in postmenopausal women[3, 36] while two later studies found comparable effects between the two bisphosphonates.[37, 38] Unable to account for

confounding from unmeasured variables such as frailty and healthy behaviors may contribute to bias in comparative effectiveness studies of alendronate and risedronate.

Instrumental variables (IVs) have been introduced as a way to address measured and unmeasured confounding in observational studies[6] and the IV approach is gaining popularity in prescription drug research.[46] The IV analysis can approximate randomization by identifying an IV or IVs that satisfy restricted assumptions: 1) the IV is highly associated with treatment choice; 2) is independent of measured and unmeasured cofounders and 3) does not directly cause a patient outcome.[44, 99]

The objectives of this study were to 1) assess the comparative effectiveness of alendronate vs. risedronate on the risk of 12-month non-vertebral fractures in women 50 years of age or older using an IV approach and 2) apply two IVs and compare their performance in evaluating the same question in the same population.

4.2 Methods

4.2.1 Data Source

This study used the Medstat MarketScan Commercial Claims and Encounters (CCE) and Medicare Supplemental Database (Ann Arbor, MI). Data were available for 2005-2009 and partially for 2010. The MarketScan database captures the largest convenient sample of over 73 million unique patients. Since 1996, it has collected information mostly from large employers in the U.S. [71] This nationwide database contains over 500 million claim records per year from individuals with employer-

sponsored health insurance. Information captured in the database includes patient demographics, detailed enrollment, inpatient services, physician encounters and pharmacy claims. Scientific studies based on this data source have been reported in more than 100 peer-reviewed articles[71].

4.2.2 Study Design and Population

We conducted a retrospective cohort study and adopted a new user design.[76] **Figure 4-1** shows the sample selection strategy. We selected women, 50 years of age or older, who had enrollment information between 2007 and 2009 (N=8,034,624). We then identified women who initiated an oral alendronate (10mg or 70mg) or risedronate (5mg or 35mg) during the time period and had continuous enrollment before and after the index date ─ date of initiation of an alendronate or risedronate (N=360,857). Individuals were excluded if: 1) they had a bisphosphonate within 12 months before the index date and a bisphosphonate other than the study medications within 12 months after the index date (N=261,561); and 2) they had a diagnosis of Paget's disease (ICD-9-CM code: 731.0) or malignant neoplasm (ICD-9-CM: 140-208) within one year before the index date (N=11,498). Finally we restricted our sample to women who had information on physician preference. The analytic sample included 3,190 women, among whom 2,332 initiated an alendronate and 858 risedronate.

Outcome

The main outcome variable was an indicator of non-vertebral fracture (including hip, wrist/forearm and proximal humerus) identified during the first 3 and 12 months following the index date. We used diagnostic and procedure codes from claims to identify non-vertebral fractures based on approaches described by previous research[38, 78] (**appendix I** shows diagnostic and procedure codes).

Main Exploratory Variable

The main exploratory variable was an indicator of alendronate (10mg or 70mg) or risedronate (5mg or 35mg). We identified alendronate or risedronate using the national drug code (NDC) and **appendix II** shows the codes.

Covariates

We determined patient demographic characteristics at the index date and other characteristics using claims from inpatient services, outpatient services and pharmacy claims within 12 months before the index date (**appendix III**). The characteristics included: 1) patient demographic (age); 2) history of non-vertebral fracture and diagnosis of osteoporosis; 3) co-morbidity measured by the Diagnostic Cost Group Hierarchical Condition Category (DCG/HCC) classification system (DxCG, Boston, MA)[88]; 4) co-medications (drugs that may cause osteoporosis, treat/prevent osteoporosis and drugs associated with fracture); 5) health services utilization (hospitalization and screening

mammogram); 6) geographic location of primary beneficiary's residence; and 7) types of health plans.

We measured patient's age in years. For patient history, a diagnosis of osteoporosis was defined as having a diagnostic code of 733.0x[38]. We defined history of non-vertebral fracture as having a diagnosis of hip fracture, wrist/forearm or proximal humerus within a year prior to the index date. We measured co-morbid condition using the DCG/HCC classification system. The DCG/HCC risk adjuster creates a single score for each person based on the presence of 189 medical conditions in the diagnosis fields of claims records. Despite its development for Medicare billing purpose, the DCG/HCC has been widely applied as a measure of confounding in studies of drug use[89]. We grouped concomitant medications based on their relationships with osteoporosis and fracture. Drugs that may cause osteoporosis included glucocorticoids[90], H2 inhibitors, proton pump inhibitors (PPI)[91] and thyroid medications[92]. Drugs that treat or prevent osteoporosis included calcitonin, vitamin D, estrogen, selective estrogen receptor modulator (SERM) and parathyroid hormone[15]. Drugs that may be associated with fracture included psychotropic medications (benzodiazepine, selective serotonin reuptake inhibitor [SSRI], non-SSRI antipsychotic, anticonvulsant and hypnotics)[93], cardiovascular medications (beta blocker and thiazide)[94, 95], and anti-inflammatory drugs (non-steroidal anti-inflammatory drug [NSAID] and cyclooxygenase 2 [COX2] inhibitor). Health services utilization variables included any hospitalization and any screening mammogram as proxy for health behavior. We categorized geographic location of primary beneficiary's residence into north central, northeast, south and west. Types of health

plans included comprehensive plan, health maintenance organization (HMO), point of service (POS), and preferred provider organization (PPO). A detailed list of covariates can be found in the **appendix III**.

Instrumental Variables

We used two IVs in this study. We have proposed a new IV for comparative effectiveness research in a previous paper (discussed in Aim 1). The IV we used was based on calendar time, specifically, the date of generic alendronate availability. Fosamax (alendronate) went off patent protection in February 2008; so the IV was defined as an indicator of time before or after February 1, 2008. Theoretically, the date of generic alendronate availability satisfies key assumptions of a valid IV. First, the use of a drug will increase after its patent protection expires partially because of the drop in price.[97] Generic alendronate has been on the market since February 2008, while the patent of Actonel (brand name for risedronate) has not expired yet. Therefore, the use of alendronate in comparison to risedronate would increase after alendronate went generic. Second, a historical date is independent of the characteristics of a population because they do not change over a short time period. In addition, a historical date does not directly cause patient outcome. Therefore the date of generic alendronate availability is a valid IV.

We also used a physician preference IV that has been applied in several studies examining the comparative effectiveness of prescription drugs (i.e. atypical vs. typical antipsychotics).[48, 61, 63] We adapted a method based on Brookhart et al. to measure

physician preference [45] - namely the most recent new bisphosphonate prescription for a prescriber's patient other than the present patient. Since prescriber information was only available in inpatient and outpatient claims but not pharmacy claims, we develop restrict criteria to measure physician preference in our data. We first identified the physician who saw the study patient at the index date. We then identified all patients with at least one bisphosphonate prescription of the physician within a year before the index date. Finally, the closest bisphosphonate prescription to the index date was considered as the physician's preference.

4.2.3 Statistical Analysis

Descriptive Statistics

We presented means and standard deviations for continuous variables, and frequencies and proportions for discrete variables. We described the distribution of patient characteristics by the original treatment assignment (alendronate and risedronate) and then by levels of the IVs. We compared means using t-test and proportions using Chi-square test or Fisher's exact test.

Conventional Univariate and Multivariate analyses

We examined the crude association between study bisphosphonates and non-vertebral fracture outcome at 12 months using ordinary least squares linear regressions. We also conducted multiple linear regressions to assess the association adjusting for variables described in the covariates section. We reported risk differences (RDs) from

the linear regressions. The reason we chose linear regression instead of logistic regression was that linear reports RD which can be used to compare results between the conventional analyses and the IV analyses.[48]

Instrumental Variables (IV) Analysis

We used a 2-stage least square (2SLS) regression[44] for the IV analysis and RDs were reported. We presented the IV analysis for the calendar time IV as an example. We built two simultaneous equations (equation 1 and 2). In the first stage (equation 1), we regressed the treatment variable on the IV and other measured covariates. In equation 1, E[T|IV] indicates the expected value of the treatment assignment for the i^{th} patient given the IV after controlling for measured covariates. T equals 1 when the patient receives an alendronate and 0 otherwise. IV is the date of generic alendronate availability. It equals 1 when the date is after February 1, 2008 and 0 otherwise. X is a vector of measured covariates. $\hat{\alpha}_1$ estimates the increase of the probability of initiating an alendronate after it turns generic adjusting for other measured covariates.

In the second stage (equation 2), we regressed the outcome on the expected values of treatment assignment (E[T|IV]) obtained from the first stage and other measured covariates. Y_i represents the outcome of the i^{th} patient, an indicator of non-vertebral fracture. It equals 1 when a patient has at least one non-vertebral fracture and 0 otherwise. $\hat{\beta}_1$ is the IV estimator.

Equation (1)

$$E[T \mid IV] = \Pr(T_i = 1 \mid IV_{i,} X_i) = \alpha_0 + \alpha_1 IV + \sum_{j=2}^{m} \alpha_j X_{ji}$$

Equation (2)

$$E[Y \mid IV] = \Pr(Y_i = 1 \mid \Pr(T_i = 1 \mid IV_i, X_i), X_i) = \beta_0 + \beta_1 \Pr(T_i = 1 \mid IV_i, X_i) + \sum_{j=2}^{m} \beta_j X_{ji}$$

We also conducted the two stage residual inclusion (2SRI) for the IV analysis because studies have shown that the 2SRI is consistent in a generic parametric framework and it is robust to nonlinearity while the 2SLS is not.[100] The difference between the 2SRI and 2SLS is that we do not replace the treatment variable with the expected values from the first stage regression. We, instead, adjust the residuals from the first stage in the second stage model. We yielded similar results from both 2SRI and 2SLS and reported results from the 2SLS in this study.

Comparison of the IVs

We compared the performance of the two IVs based on empirical evidence of the assumptions of a valid IV. First, we examined the strength of the IV by reporting F statistics from the first stage of the 2SLS. A valid IV should have F statistic ≥ 10.[80] A greater F statistic also indicates a stronger IV. Second, we assessed the ability of both IVs to balance measured patient characteristics. A stronger IV should be associated with fewer measured confounders.[81] Finally, the assumption that a valid IV should not directly cause a patient outcome is not verifiable. We adopted a method by Newhouse

and McClellan[6] to indirectly verify this assumption. We assessed whether the IVs were able to keep balance in short-term outcomes (i.e. 3-month non-vertebral fracture) that cannot be affected by the medical intervention (bisphosphonates).

All analyses were performed using STATA 10. We used IVREG2 for the IV analysis. The study was approved by the Institutional Review Board of the University of Massachusetts Medical School.

4.3 Results

We identified 3,190 women, 50 year of age or older, who were treated by 1,678 physicians. The average age was 63 year old. About 3.5% of women had a history of non-vertebral fracture and 29% had at least one diagnosis of osteoporosis before initiation of a study bisphosphonate. The average co-morbidity score (DCG/HCC) was approximately 0.57.

Table 4-1 shows the distribution of patient characteristics between women initiating an alendronate and those initiating a risedronate. We found that compared with women initiating an alendronate those initiating a risedronate were older (62 vs. 64 years old; $P < 0.01$) and had a greater co-morbidity score (DCG/HCC: 0.56 vs. 0.59; $P < 0.01$). Women initiating a risedronate also more often received thyroid drugs (18.14% vs. 21.33%; $P<0.05$), but less often received vitamin D (14.92% vs. 3.85%; $P<0.01$), benzodiazepine (18.83% vs. 14.57%; $P<0.01$) or NSAIDS/Cox-2 inhibitors (30.83% vs. 25.64%; $P<0.01$). Women initiating a risedronate were more likely located in the south

and in a PPO while those imitating an alendronate were more likely located in the west and in a HMO.

4.3.1 Conventional Analysis

In the conventional analysis (adjusted and unadjusted analysis for the original treatment assignment in **Table 4- 2**), we found that alendronate and risedronate had comparable effects on the risk of non-vertebral fractures. The results indicated that for every 100 women treated with an alendronate we would expect 0.6 (RD=-0.6) fewer fracture cases (95%CI -2.00-1.00) had they been treated with a risedronate. After adjusting for covariates, the RD reduced to -0.4 cases per 100 women and it was also not statistically significant.

4.3.2 Instrumental Variable Analysis

The IV analysis with calendar time IV (adjusted and unadjusted analyses for the date of generic alendronate availability in **Table 4- 2**) estimated that compared to risedronate alendronate reduced the risk of non-vertebral fractures by 2.1 cases per 100 women (RD: -2.1; 95% CI: -8.00-4.00). After adjusting for covariates the RD increased to 2.9 (RD=-2.9; 95%CI: -8.00-2.00). Both RDs were not statistically significant.

The IV analysis with physician preference IV (adjusted and unadjusted analyses for physician preference in **Table 4-2**) showed that compared to risedronate alendronate reduced the risk of non-vertebral fractures by 5.8 cases per 100 women (RD: -5.8;

95%CI: -12.00-1.00). In the adjusted model, the RD was -4.8 cases per 100 women (95%CI: -12.00-3.00). Both RDs were not statistically significant.

4.3.3 Comparison of the IVs: Strength of the IVs

Table 4-3 shows the strength of the IVs in inducing the variation of the treatment choice. We found that both IVs were strongly associated with the treatment choice (both F statistics >10). The IV1 (date of generic alendronate availability) explained more of the variation of the treatment choice than IV2 (physician preference) because it had a greater F statistic. The F statistic for the IV1 was 200 ($P<0.01$) and it was 96 for IV2 ($P<0.01$).

4.3.4 Comparison of the IVs: Balance of Measured Characteristics

Tables 4-1 and 4-4 show the ability to balance measured patient characteristics with and without the IV1. We found that the IV1 was associated with fewer patient characteristics than the original treatment assignment. For instance, without the IV1 the original treatment was associated with seven patient characteristics including age, DCG/HCC, thyroid drug, vitamin D, benzodiazepine, NSAIDS/Cox-2 inhibitor, geography and health plan type. However, the IV1 was associated with 6 patient characteristics including H2 inhibitor, proton pump inhibitor, vitamin D, geography, health plan type and mammogram.

Tables 4-1 and 4-5 demonstrate the balance of measured patient characteristics with and without IV2. The IV2 was associated with fewer patient characteristics than the original treatment assignment. The original treatment assignment was associated with

seven patient characteristics while the IV2 was associated with 5 characteristics including DCH/HCC, vitamin D, benzodiazepine, geography and health plan type. We concluded from **Tables 4-1**, **4-4** and **4-5** that both IV analyses provide better balance of patient characteristics than the conventional treatment analysis.

4.3.5 Comparison of the IVs: Direct Association with the Outcome

Table 4-6 shows the balance of 3-month non-vertebral fractures with and without IVs as a proxy for testing whether the IV directly causes the patient outcome. We found that the 3-month non-vertebral fracture was not associated with the original treatment assignment, IV1 and IV2. Compared to women initiating a risedronate those initiating an alendronate had a lower but not statistically significant risk of 3-month non-vertebral fractures (1.76% vs. 1.98; $P > 0.05$). Compared to women who initiated a study bisphosphonate before February 1st, 2008, those initiating a study bisphosphonate after the date had a lower but not statistically significant rate of 3-month non-vertebral fractures (1.89% vs. 1.73%; $P > 0.05$). Similarly, women whose prescribers had a preference of alendronate had a lower but not statistically significant rate of 3-month non-vertebral fractures than those whose prescribers had a preference of risedronate.

4.4 Discussion

In this study, we examined the comparative effectiveness of alendronate and risedronate on the risk of non-vertebral fractures at 12 months in women 50 years of age or older. We found that conventional analyses showed no difference between the two

bisphosphonates in the effectiveness on the risk of non-vertebral fracture. Compared to risedronate alendronate reduced the risk of 12-month non-vertebral fractures by 0.6 and 0.4 cases per 100 women in the unadjusted and adjusted models respectively but neither of these effects were statistically significant. However, since this was an observational study using administrative data, we were not able to adjust important patient characteristics such as frailty and healthy behaviors that might be associated with both the treatment and the outcome. When we accounted for residual confounding from unmeasured variables using IV analyses we found similar results regardless of the IV. In the IV analysis using calendar time IV, we found that compared to risedronate alendronate reduced the risk of 12-month non-vertebral fractures by 2.9 cases per 100 women after adjusting for measured covariates and such an association was not statistically significant. For another, in the analysis with the physician preference IV, we found that compared to risedronate alendronate had a lower but not statistically significant risk reduction in 12-month non-vertebral fractures (RD: -4.8; 95%CI: -12.00-3.00).

Previous studies have presented several IVs in prescription drug research.[56, 59, 61, 62, 64, 67] Researchers have shown that the performance of IVs varies in examining different questions or the same question in different populations. For example, physician preference may be a strong and valid IV to assess the comparative effectiveness of antipsychotics in the elderly population.[63] However, the IV, nursing home prescribing preference, performed better than physician preference in assessing the same question in a nursing home population.[101] Understanding the practical and empirical advantages or

disadvantages of IVs may help researchers to solidify the validity of their IV analyses. Furthermore, it is unknown whether two valid IVs would have similar performance in addressing the same question in the same population.

In our secondary objective to assess the performance of the two IVs, we drew the following conclusions. While the overall interpretation of the IV analyses using both IVs did not differ from the conventional analysis, there are differences in empirical evidence regarding the validity of the IVs. The calendar time IV (the date of generic alendronate availability) explained more of the variation of the treatment choice than did the physician preference IV. The F statistic for the date of generic alendronate availability was 200 while it was 96 for the physician preference. This indicated that the calendar time instrument might be a stronger IV than the physician preference instrument in this specific case. Furthermore, a weaker IV may result in an overestimate of the true risk difference.[101, 102] We found that the adjusted RD for the physician preference IV was -4.8 which was greater than that found using the calendar time IV (RD=-2.8). Finally, the IV estimate based on physician preference had a wider 95% confidence interval relative to that found based on the calendar time IV. This effect has been seen in previous studies that found a wider confidence interval of the IV estimate as a consequence of applying a weaker IV.[102]

Studies have shown that a valid IV should also balance measured patient characteristics.[81] In our study, patient characteristics were evenly distributed with IVs. Fewer characteristics were significantly associated with the IVs than with the original

treatment. The calendar time IV was associated with 6 measured characteristics while the physician preference IV was associated with 5. This suggested that both IV were able to impose balance of measured patient characteristics; however, we could not rule out residual confounding since both IVs were still associated with some measured characteristics.

Another important yet unverifiable assumption of a valid IV is that the IV should not directly cause a patient outcome. As a proxy test for this assumption, we examined the association between the IV and a short-term outcome (3-month non-vertebral fractures) unaffected by the treatment as suggested by Newhouse and McClleuar.[6] We found that both IVs were not significantly associated with 3-month non-vertebral fractures. This outcome was also more evenly distributed between levels of the IVs than between two original treatment groups.

In addition to the differences in empirical evidence of a valid IV, the two IVs differ in the application in administrative data. Physician preference cannot be directly measured in administrative data. Proxy measures[103] such as the one used in this study requires information to identify prescribing physicians. A previous study has shown that the medical license number could reliably identify the prescribing physician.[104] However, the database that captures information on the medical license number is not free of charge. Furthermore, most administrative data do not have linkable information to the medical license number. This may prevent researchers from applying the physician IV. On the other hand, the calendar time IV, the date of generic availability, is easy to

apply because it does not require external data. However, this IV is limited to comparison between a generic and a brand name drug. It cannot be used to compare two brand name drugs.

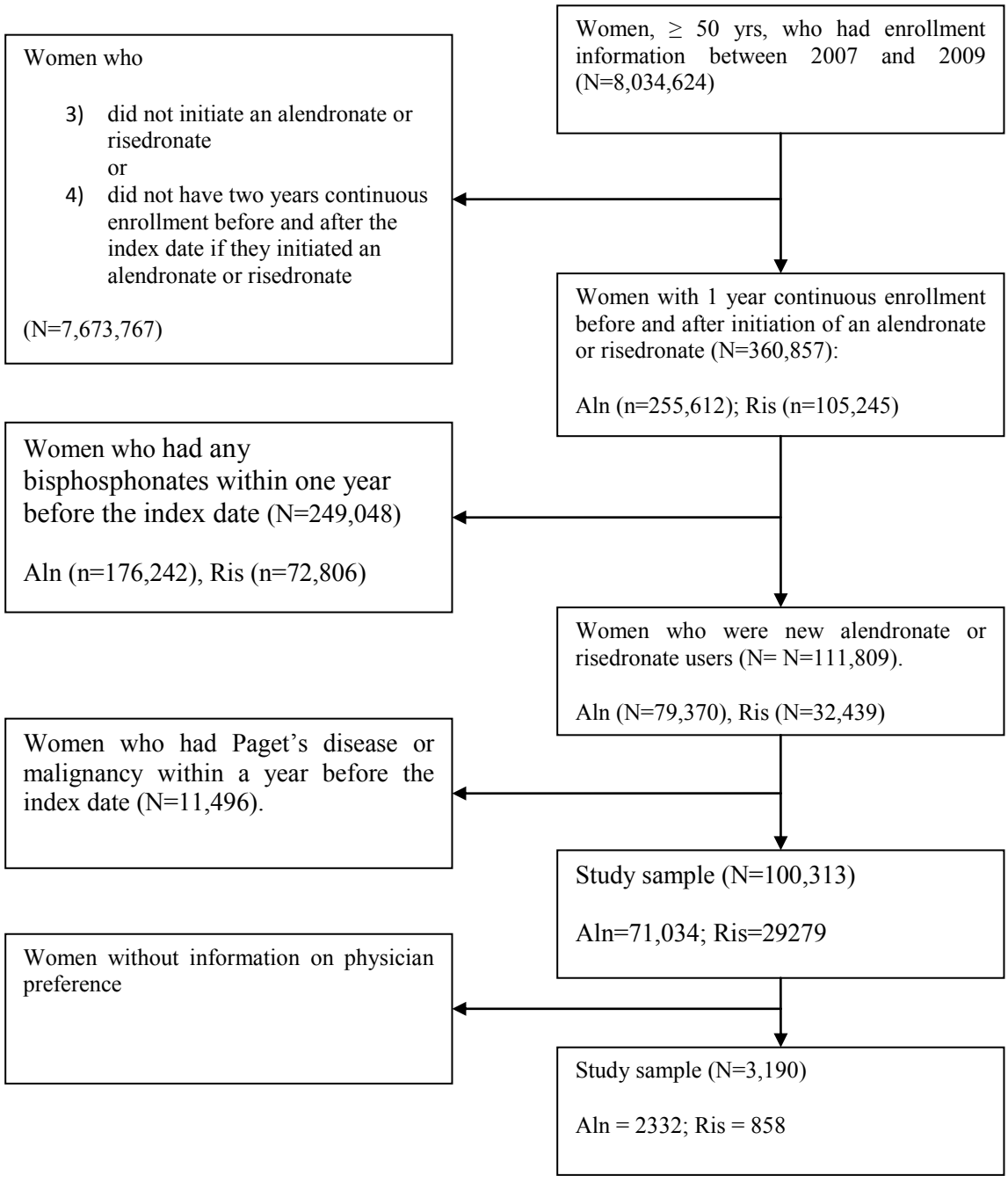
This study has several limitations. First, we used data from an insured and employed population in the US. The results may not be generalizable to uninsured and unemployed population. In fact the IV, the date of generic availability, may perform better in an uninsured and unemployed population because such a population may be more sensitive to the price reduction of generics which may induce a greater variation in the choice of medication before and after the date of generic availability. Second we adapted a method to measure physician preference based on our data because we did not have information on the prescribing physician in pharmacy claims. This suggests that misclassification of the physician preference is possible. Our proxy measure also resulted in the deletion of many subjects due to incomplete information. Third, previous studies have shown that physician preference IV would have better performance if researchers only included primary care physicians because physician specialty may be a confounder that is associated with both the treatment choice and the patient outcome.[45] However, in our dataset we could not differentiate primary care physicians from specialty physicians. This might reduce the performance of the physician preference IV in our study.

Despite these limitations, our study contributes to the literature in several ways. First, in the absence of head-to-head trials we provided further evidence that alendronate

and risedronate have a comparable effect on the risk of non-vertebral fractures at 12 months in women 50 years of age or older. Second, we applied the IV analysis to address unmeasured confounding which has not been applied in previous studies examining this question. Third, we applied a new calendar time IV (the date of generic availability) and compared it to an existing IV (the physician preference). We found that both IVs are valid in this specific study based on empirical evidence of a valid IV. Fourth, we found that the calendar IV was a stronger IV in explaining the variation of the treatment choice than the physician preference IV. Both IVs had similar performance in reducing imbalance of measured patient characteristics and did not directly cause the outcome. Finally, the calendar IV may be more practical than the physician preference IV because it did not require external information to be measured accurately; thus is relatively easier to apply.

In conclusion, IV analysis may be useful to estimate the comparative effectiveness between alendronate and risedronate on the risk of 12-month non-vertebral fractures in women older than 50 years. The new calendar time IV based on the date of generic availability appears to be valid in this specific case. It may be practically easier to use the calendar time IV than the physician preference IV.

Figure 4-1: Sample Selection Strategy *



***Aln=Alendronate, Ris =Risedronate**

Table 4-1: Distribution of Patient Characteristics Stratified by Treatment Assignment*

Characteristics	Alendronate		Risedronate		P value
Total	2332		858		
Age (mean, sd)	62.42	(9.80)	63.77	(10.44)	<0.01
History of fracture	81	(3.47)	31	(3.61)	
Osteoporosis	683	(29.29)	228	(26.57)	
DCG/HCC (mean, sd)	0.56	(0.48)	0.59	(0.46)	<0.01
Drug that cause osteoporosis					
Glucocorticoid	671	(28.77)	256	(29.84)	
H2 inhibitor	108	(4.63)	39	(4.55)	
Proton pump inhibitor	415	(17.80)	143	(16.67)	
Thyroid drug	423	(18.14)	183	(21.33)	<0.05
Drugs that treat/prevent osteoporosis					
Vitamin D	348	(14.92)	33	(3.85)	<0.01
Estrogen	335	(14.37)	143	(16.67)	
SERMS	72	(3.09)	22	(2.56)	
Parathyroid hormone	14	(0.60)	4	(0.47)	
Calcitonin	19	(0.81)	9	(1.05)	
Drugs associated with fracture					
Benzodiazepine	439	(18.83)	125	(14.57)	<0.01
SSRI/Non-SSRI	722	(30.96)	263	(30.65)	
Anticonvulsant	183	(7.85)	68	(7.93)	
Hypnotics	316	(13.55)	130	(15.15)	
B blocker	472	(20.24)	190	(22.14)	
Thiazide	221	(9.48)	83	(9.67)	
NSAIDS/Cox-2 inhibitor	719	(30.83)	220	(25.64)	<0.01
Geography¶					<0.01
North Central	415	(17.80)	123	(14.34)	
, Northeast	89	(3.82)	24	(2.80)	
South	1093	(46.87)	590	(68.76)	
West	733	(31.43)	120	(13.99)	
Health Plan type¶					<0.05
Comprehensive	86	(3.69)	31	(3.61)	
HMO	1123	(48.16)	361	(42.07)	
POS	131	(5.62)	59	(6.88)	
PPO	955	(40.95)	391	(45.57)	
Health service utilization					
Hospitalization	259	(11.11)	96	(11.19)	
Mammogram	1353	(58.02)	466	(54.31)	

* Data are given as number (percentage) unless otherwise indicated.
¶ Numbers do not add to 100% because of missing data
DCG/HCC= Diagnostic Cost Group Hierarchical Condition Category; SSRI=selective serotonin reuptake inhibitor; NSAIDS=non-steroidal anti-inflammatory drug; Cox-2=cyclooxygenase-2; HMO=Health Maintenance Organization; POS=Point of Service; PPO=Preferred Provider Organization

Table 4-2: Comparing the Effect of Alendronate vs. Risedronate on the Risk of Non-vertebral Fractures in 12 Month

Unadjusted	**Risk difference**	**95% Confidence interval**
Original treatment assignment	-0.6	(-2.00-1.00)
IV1 (date of generic availability)	-2.1	(-8.00-4.00)
IV2 (physician preference)	-5.8	(-12.00-1.00)
Adjusted¶		
Original treatment assignment	-0.4	(-2.00-1.00)
IV1 (date of generic availability)	-2.9	(-8.00-2.00)
IV2 (physician preference)	-4.6	(-12.00-3.00)

¶Adjusting for covariates including demographic characteristics, osteoporosis related factors, co-morbidity, concomitant medications, health services utilization region of residence and health plan types.

Table 4-3: Strength of the IVs in Predicting Treatment Choice*

	Partial F statistic	**Partial R square**	**P Value**
IV1 (date of generic availability)	200	0.06	<0.01
IV2 (physician preference)	96	0.03	<0.01
* Adjusting for covariates including demographics, osteoporosis related factors, co-morbidity, medications, health services utilization, region of residence and health plan types.			

Table 4-4: Distribution of Patient Characteristics Before and After Feb, 2008*

Characteristics	Before Feb, 2008		After Feb, 2008		P value
Total	1801		1389		
Age (mean, sd)	62.89	(10.29)	62.64	(9.75)	
History of fracture	59	(3.28)	53	(3.82)	
osteoporosis	491	(27.26)	420	(30.24)	
DCG/HCC (mean, sd)	0.57	(0.49)	0.56	(0.46)	
Drug that cause osteoporosis					
Glucocorticoid	527	(29.26)	400	(28.80)	
H2 inhibitor	69	(3.83)	78	(5.62)	<0.05
Proton pump inhibitor	291	(16.16)	267	(19.22)	<0.05
Thyroid drug	341	(18.93)	265	(19.08)	
Drugs that treat/prevent osteoporosis					
Vitamin D	276	(15.32)	105	(7.56)	<0.01
Estrogen	289	(16.05)	189	(13.61)	
SERMS	55	(3.05)	39	(2.81)	
Parathyroid hormone	13	(0.72)	5	(0.36)	
Calcitonin	19	(1.05)	9	(0.65)	
Drugs associated with fracture					
Benzodiazepine	300	(16.66)	264	(19.01)	
SSRI/Non-SSRI	551	(30.59)	434	(31.25)	
Anticonvulsant	132	(7.33)	119	(8.57)	
Hypnotics	238	(13.21)	208	(14.97)	
B blocker	359	(19.93)	303	(21.81)	
Thiazide	163	(9.05)	141	(10.15)	
NSAIDS/Cox-2 inhibitor	506	(28.10)	433	(31.17)	
Geography¶					<0.01
North Central	289	(16.05)	249	(17.93)	
Northeast	75	(4.16)	38	(2.74)	
South	1030	(57.19)	653	(47.01)	
West	406	(22.54)	447	(32.18)	
Health Plan type¶					<0.01
Comprehensive	61	(3.39)	56	(4.03)	
HMO	729	(40.48)	755	(54.36)	
POS	113	(6.27)	77	(5.54)	
PPO	881	(48.92)	465	(33.48)	
Health service utilization					
Hospitalization	192	(10.66)	163	(11.74)	
Mammogram	981	(54.47)	838	(60.33)	<0.01

* Data are given as number (percentage) unless otherwise indicated.
¶ Numbers do not add to 100% because of missing data
DCG/HCC= Diagnostic Cost Group Hierarchical Condition Category; SSRI=selective serotonin reuptake inhibitor; NSAIDS=non-steroidal anti-inflammatory drug; Cox-2=cyclooxygenase-2; HMO=Health Maintenance Organization; POS=Point of Service; PPO=Preferred Provider Organization

Table 4-5: Distribution of Patient Characteristics Stratified by Physician Preference*

Characteristics	Physician preference				P value
	Alendronate		Risedronate		
Total	2053		1137		
Age (mean, sd)	62.35	(9.83)	63.56	(10.14)	
History of fracture	69	(3.36)	43	(3.78)	
osteoporosis	590	(28.74)	321	(28.23)	
DCG/HCC (mean, sd)	0.56	(0.46)	0.59	(0.51)	<0.01
Drug that cause osteoporosis					
Glucocorticoid	595	(28.98)	332	(29.20)	
H2 inhibitor	93	(4.53)	54	(4.75)	
Proton pump inhibitor	379	(18.46)	179	(15.74)	
Thyroid drug	387	(18.85)	219	(19.26)	
Drugs that treat/prevent osteoporosis					
Vitamin D	270	(13.15)	111	(9.76)	<0.01
Estrogen	302	(14.71)	176	(15.48)	
SERMS	59	(2.87)	35	(3.08)	
Parathyroid hormone	13	(0.63)	5	(0.44)	
Calcitonin	21	(1.02)	7	(0.62)	
Drugs associated with fracture					
Benzodiazepine	402	(19.58)	162	(14.25)	<0.01
SSRI/Non-SSRI	644	(31.37)	341	(29.99)	
Anticonvulsant	176	(8.57)	75	(6.60)	
Hypnotics	290	(14.13)	156	(13.72)	
B blocker	437	(21.29)	225	(19.79)	
Thiazide	190	(9.25)	114	(10.03)	
NSAIDS/Cox-2 inhibitor	613	(29.86)	326	(28.67)	
Geography¶					<0.01
North Central	352	(17.15)	186	(16.36)	
Northeast	83	(4.04)	30	(2.64)	
South	962	(46.86)	721	(63.41)	
West	653	(31.81)	200	(17.59)	
Health Plan type¶					<0.05
Comprehensive	84	(4.09)	33	(2.90)	
HMO	942	(45.88)	542	(47.67)	
POS	105	(5.11)	85	(7.48)	
PPO	890	(43.35)	456	(40.11)	
Health service utilization					
Hospitalization	237	(11.54)	118	(10.38)	
Mammogram	1182	(57.57)	637	(56.02)	

* Data are given as number (percentage) unless otherwise indicated.
¶ Numbers do not add to 100% because of missing data
DCG/HCC= Diagnostic Cost Group Hierarchical Condition Category; SSRI=selective

serotonin reuptake inhibitor; NSAIDS=non-steroidal anti-inflammatory drug; Cox-2=cyclooxygenase-2; HMO=Health Maintenance Organization; POS=Point of Service; PPO=Preferred Provider Organization

Table 4-6: Balance of 3-Month Non-vertebral Fracture With and Without IVs*

3-month non-vertebral fracture	**Original treatment**		
	Alendronate	Risedronate	P values
	1.76	1.98	>0.05
	IV1: date of generic availability		
	Before Feb, 2008	After Feb, 2008	P value
	1.89	1.73	>0.05
	IV2: physician preference		
	Alendronate	Risedronate	P value
	1.75	1.93	>0.05
*IV: Instrumental variable			

5 CHAPTER V: CONCLUSIONS

The objectives of this dissertation were to 1) proposed a novel IV for the comparative effectiveness research of prescription drugs (**Chapter II**); 2) explore the use of the IV analysis to assess the comparative effectiveness of alendronate and risedronate on the risk of non-vertebral fracture in older women (**Chapter III**) and 3) compare the proposed IV with an existing valid IV in order to investigate the performance of two individual IVs when we applied them to the same question in the same population (**Chapter IV**).

5.1 Chapter II: Date of Generic Availability - A Potential Instrumental Variable in the Comparative Effectiveness Research of Prescription Drugs

The objective of this study was to introduce a novel IV, the date of generic availability, and assess the validity of the proposed IV in a case study of bisphosphonates. We provided logic arguments as well as empirical evidence to support the validity of this IV. The study emphasized on assessing the performance of the IV on the key assumptions of a valid IV. First, we reasoned that the date of generic availability would be associated with patient treatment choice due to the lower price of the generic equivalent. In the case study, we found that IV was strongly associated with treatment choice in one comparison (alendronate vs. risedronate) but not the other (alendronate vs. placebo).

Second, we argued that the proposed IV was not directly and indirectly associated with the patient outcome except through the treatment assignment. Since the date of generic availability is a calendar time IV, any residual confounding can only occur by

factors that vary at the exact same time as the IV. Similarly, the date of generic availability is unlikely to have direct effect on patient outcomes (i.e. fracture). In the case study, we demonstrated that the IV was able to balance measured patient characteristics implying that it could also impose balance on unmeasured confounders. We further showed that the IV did not directly cause the outcome because the IV was not associated with the 3 month non-vertebral fracture. Comparing with the original treatment assignment, the IV provided more balance of the 3 month non-vertebral fracture.

The evidence of this study supported the validity of the date of generic availability as an IV in the study of bisphosphonates. Future research is warranted to explore the validity of this IV in other therapeutic areas. Furthermore, since only a limited number of pharmaceutical companies are allowed to manufacture the generic equivalents within some six months period after patent expiration, the price of such a generic version may not be substantially different from its brand name during the first six months. As a result, the entry of generic equivalents of a brand name drug may not show significant impact on the treatment choice right after the patent expiration. Future research may consider alternative IVs such as 6 month or even 12 months after the date of generic availability because it is possible that the longer a generic drug is on the market, the higher likelihood that patients will adopt this medication.

5.2 Chapter III: Comparative Effectiveness of Alendronate and Risedronate on Non-Vertebral Fractures: An Instrumental Variable Analysis

The objective of this study was to assess the comparative effectiveness of alendronate vs. risedronate on the risk of non-vertebral fractures in women, 50 years of age or older, using claims data from multiple health plans across the US. Since generic alendronate was available in February 2008 while Actonel (risedronate) is still under patent protection, the comparative effectiveness evidence of alendronate vs. risedronate on the risk non-vertebral fractures may help physicians and patients to choose a cost-effectiveness strategy to treat osteoporosis and prevent osteoporotic fractures. However, existing evidence from observational studies was inconsistent. Possible reason of such an inconsistency might come from the fact that previous observational studies were not able to address unmeasured confounders. Therefore, in this study we applied an IV analysis to address confounding from unmeasured variables beside the conventional analysis. Our conventional analysis showed a comparable effect of alendronate vs. risedronate on the risk of non-vertebral fracture at 6 months and 12 months. The results of the IV analysis were consistent with those from the conventional analysis. Therefore, our study supported that alendronate and risedronate were comparable to reduce the risk of 12-month non-vertebral fractures in older women. Since generic alendronate is availability on the market while generic risedronate is not, promoting the use of alendronate may help reduce the healthcare cost and not sacrifice the clinical effectiveness.

5.3 Chapter IV: Comparative Effectiveness of Alendronate and Risedronate on the Risk of Non-vertebral Fractures: Using Two Valid Instrumental Variables

In this study, we compared the performance of two IVs (the date of generic alendronate availability vs. physician preference) to assess the comparative effectiveness of alendronate vs. risedronate on the risk of non-vertebral fractures in women 50 years of age or older. We found IV analyses using both IVs reached the same conclusion that alendronate and risedronate were comparable to reduce the risk of non-vertebral fractures and these results were consistent with the conventional analysis. However, the performance of the two IV was different. Based on empirical evidence of a valid IV, we found that the calendar time IV explained more of the variation of the treatment choice than did the physician preference IV. The physician preference IV also provided greater point estimates and wider confidence interval relative to the calendar time IV. Furthermore, both IVs could balance of measured patient characteristics. We found that fewer characteristics were significantly associated with the IVs than with the original treatment. However, we could not rule out residual confounding from unmeasured variables. Finally, both IVs also showed indirect evidence of not being associated with the patient outcome. In general, evidence supported that both IVs were valid in assessing the comparative effectiveness of alendronate vs. risedronate on the risk of non-vertebral fractures in older women. However, the physician preference IV was a weaker IV in this case.

We also evaluated the practical advantages and disadvantages of both IVs. Physician preference could not be directly measured in administrative data. Proxy

measures such as the one used in this study requires information to identify prescribing physicians. A previous study has shown that the medical license number could reliably identify the prescribing physician. However, most administrative data do not have linkable information to the medical license number. This may prevent researchers from applying the physician IV. On the other hand, the calendar time IV, the date of generic availability, is easy to apply because it does not require external data. However, this IV is limited to comparison between a generic and a brand name drug. It cannot be used to compare two brand name drugs. We concluded that IV analysis might be useful to estimate the comparative effectiveness between alendronate and risedronate on the risk of non-vertebral fractures in women older than 50 years. The calendar time IV based on the date of generic availability and the physician preference appeared to be valid in this specific case. It might be practically easier to use the calendar time IV than the physician preference IV.

5.4 Strengths and Limitations

Strengths

1. The limited existing evidence of the comparative effectiveness between alendronate and risedronate on the risk of non-vertebral fractures was mixed. The study extended the existing evidence pool.

2. The study utilized a large nationwide sample from the MarketScan databases. The sample size might be more representative than those used in the previous studies.

3. IV analysis may provide more correct estimates because it controls for both measured and unmeasured confounders.

4. The IV proposed in the study may be useful for research on other prescription drugs in the future.

Limitations

1. Although the study samples were drawn from the large convenience sample from large employers in the U.S., The results may not be generalizable to uninsured and unemployed population. In fact the IV, the date of generic availability, may perform better in an uninsured and unemployed population because such a population may be more sensitive to the price reduction of generics which may induce a greater variation in the choice of medication before and after the date of generic availability.

2. In Aim 1, using ICD-9 codes to identify patients with osteoporosis or at risk for osteoporotic fractures has not been validated in previous studies. Misclassification of osteoporosis patients is possible. For instance, Yood et al. showed that only 26% of patients (n=236) had a diagnostic code associated with osteoporosis after a confirmed DXA diagnosis[10]. In order to quantify the miscalculation of osteoporosis in my study, we conducted an external study to calculate sensitivity, specificity and positive predictive value (PPV) of increasingly restricted algorithms to identify patients with osteoporosis or at risk

for osteoporotic fractures using administrative data from the Fallon Clinic. We found that the algorithm used in our study could accurately identify patients with osteoporosis or at risk for osteoporotic fractures (sensitivity= 71%, specificity = 72% and PPV=76%).

3. In Aim 3, we adapted a method to measure physician preference based on our data because we did not have information on the prescribing physician in pharmacy claims. This suggests that misclassification of the physician preference is possible. Furthermore, previous studies have shown that physician preference IV would have better performance if researchers only included primary care physicians because physician specialty may be a confounder that is associated with both the treatment choice and the patient outcome (cite). However, in our dataset we could not differentiate primary care physicians from specialty physicians. This might reduce the performance of the physician preference IV in our study.

4. The use of 2SLS for a dichotomous treatment variable and outcome may have limitations. Using linear models may produce expected values that are greater than 1 or lower than 0 and the bivariate normal distribution of errors will be violated. However, researchers have suggested that this may be a theoretical rather than a practical problem. [105]

5. The proposed IV also has limitations. First, this IV cannot be used in comparing two patent protected drugs. Second, the strength of this IV requires further

examination, especially with other prescription drugs. Our own examination revealed that the IV appeared to be weak when the comparator was a "placebo" control (no OP treatment). A possible reason is that the prescribing pattern of OP treatment may not change because of the generic availability of alendronate. Without a strong variation in the use of alendronate overtime, the first assumption of a valid IV is violated. Third, it appears that the IV, the date of generic availability, may perform best when there is strong evidence of confounding by indication; we can show that the IV not only balances observed patient characteristics but reduces the imbalance of these characteristics by original treatment groups. Moreover, it is unnecessary to apply the IV analysis without strong evidence of confounding by indication.[81] We suggest that research evaluate the performance of candidate IVs before selecting an IV for analysis.

6 APPENDIX

I. Diagnostic and procedure codes for non-vertebral fractures

Fracture site	**ICD-9**	**ICD-9 procedure**	**Current Procedural Terminology (CPT)**
Wrist	813.x, 813.4x, 813.5x,	79.02, 79.12, 79.22, 79.32	25600, 25605, 25611, 25620
Hip	820.x, 821.x	79.x5, 79.05, 79.15, 79.25, 79.35,	27230-27248
Humerus	812.20, 812.21, 812.30, 812.31,	78.12, 78.52, 79.11, 79.21, 79.31	24500, 24505, 24515, 24516

II : Identify study drugs using national drug codes (NDC)

Drug Name	NDC
Alendronate	00006003121 00006003144 00006027044 00006071021 00006071044 00006093628 00006093631 00006093658 00006093672 00006093682 00006383334 00093514101 00093514156 00093517120 00093517144 00555072051 00555072054 00591317304 16252060102 16252060144 16714063101 16714063102 16714063301 16714063302 21695090204 41616063683 41616063688 41616063868 49999050104 54569521800 54569605000 54868385700 54868446200 54868548000 54868586100 54868586200 55111058801 55111058830 55111059248 58016078800 58016078830 58016078860 58016078890 60505259301 60505259303 60505259602 60505259604 60505259608 65862032730 65862032904 68084032264 68258301401
Risedronate	00149047101 00149047103 00149047201 00149047204 00149047501 16590072104 49999044804 54868438600 54868467100 54868551800 55887068504

III. Identify patient characteristics using claims data

Characteristics	**Code**
History of non-vertebral fracture	See appendix I
Osteoporosis	ICD: 733.0x
Glucocorticoid H2 inhibior Proton pump inhibitor Thyroid drug Vitamin D Estrogen SERMS Parathyroid hormone Calcitonin Benzodiazepine SSRI/Non-SSRI Anticonvulsant Hypnotics B blocker Thiazide NSAIDS/Cox-2 inhibitor	Any claim within 12 month prior to the index date
Hospitalization Mammogram	Any claim ICD: V76.12; CPT: 77056 77057; HCPCS G0202

IV. Non-vertebral fracture between women initiating an alendronate or a risedronate, and between women initiating a bisphosphonate before and after generic alendronate availability

	Fracture	Alendronate		Risedronate		Before February 1,2008		After February 1, 2008	
6 months	Yes	1449	(2.04)	542	(1.85)	1156	(1.87)	835	(2.17)
	No	69585	(97.96)	28737	(98.15)	60601	(98.13)	37721	(97.83)
12 months	Yes	2053	(2.89)	789	(2.69)	1661	(2.69)	1181	(3.06)
	No	68981	(97.11)	28490	(97.31)	60096	(97.31)	37375	(96.94)

V: Comparing the effect of alendronate vs. risedronate on the risk of non-vertebral fracture in 6 months (multiple logistic regression result)

	RD	95% confidence interval
Alendronate vs. risedronate	0.121	-0.058 - 0.299
Demographics		
Age	0.041	0.032 - 0.051
History		
History of non-vertebral fracture	29.868	29.429 - 30.307
Osteoporosis	0.038	-0.130 - 0.206
Co-morbidity (DCG/HCC)	0.701	0.506 - 0.896
Drug that cause osteoporosis		
Glucocorticoid	-0.182	-0.370 - 0.006
H2 inhibior	0.015	-0.396 - 0.426
Proton pump inhibitor	-0.064	-0.263 - 0.136
Thyroid drug	-0.155	-0.359 - 0.049
Drugs that treat/prevent osteoporosis		
Vitamin D	-0.436	-0.652 - -0.220
Estrogen	-0.155	-0.390 - 0.080
SERMS	-0.249	-0.647 - 0.150
Parathyroid hormone	-0.671	-1.395 - 0.054
Calcitonin	-0.350	-0.982 - 0.281
Drugs associated with fracture		
Benzodiazepine	0.084	-0.136 - 0.304
SSRI/Non-SSRI	0.497	0.307 - 0.688
Anticonvulsant	-0.096	-0.415 - 0.222
Hypnotics	0.237	-0.012 - 0.486
B blocker	-0.011	-0.214 - 0.193
Thiazide	-0.114	-0.394 - 0.165
NSAIDS/Cox-2 inhibitor	-0.190	-0.377 - -0.004
Health service utilization		
Hospitalization	1.483	1.202 - 1.763
Mammogram	-0.251	-0.413 - -0.088
Geography (reference=North central)		
Northeast	0.014	-0.287 - 0.316
South	-0.239	-1.804 - 1.326
West	0.013	-0.217 - 0.243
Health Plan type (reference: comprehensive health plan)		

HMO	0.152	-0.131 - 0.435
POS	0.172	-0.174 - 0.518
PPO	0.177	-0.049 - 0.404

DCG/HCC= Diagnostic Cost Group Hierarchical Condition Category; SSRI=selective serotonin reuptake inhibitor; NSAIDS=non-steroidal anti-inflammatory drug; Cox-2=cyclooxygenase-2; HMO=Health Maintenance Organization; POS=Point of Service; PPO=Preferred Provider Organization

VI: Comparing the effect of alendronate vs. risedronate on the risk of non-vertebral fracture in 12 months (results from multiple linear regression)

	RD	95% confidence interval
Alendronate vs. risedronate	0.096	-0.119 - 0.311
Demographics		
Age	0.080	0.068 - 0.091
History		
History of non-vertebral fracture	31.592	31.061 - 32.123
Osteoporosis	0.145	-0.059 - 0.348
Co-morbidity (DCG/HCC)	1.228	0.992 - 1.464
Drug that cause osteoporosis		
Glucocorticoid	-0.276	-0.504 - -0.049
H2 inhibior	0.152	-0.345 - 0.649
Proton pump inhibitor	-0.140	-0.381 - 0.101
Thyroid drug	-0.192	-0.438 - 0.054
Drugs that treat/prevent osteoporosis		
Vitamin D	-0.421	-0.682 - -0.160
Estrogen	-0.414	-0.698 - -0.130
SERMS	-0.431	-0.913 - 0.051
Parathyroid hormone	-0.395	-1.270 - 0.481
Calcitonin	0.466	-0.297 - 1.230
Drugs associated with fracture		
Benzodiazepine	0.079	-0.188 - 0.345
SSRI/Non-SSRI	0.790	0.560 - 1.020
Anticonvulsant	-0.033	-0.418 - 0.352
Hypnotics	0.334	0.033 - 0.635
B blocker	-0.109	-0.355 - 0.137
Thiazide	-0.511	-0.849 - -0.174
NSAIDS/Cox-2 inhibitor	-0.106	-0.331 - 0.120
Health service utilization		
Hospitalization	1.543	1.204 - 1.882
Mammogram	-0.565	-0.762 - -0.368
Geography (reference=North central)		
Northeast	0.024	-0.341 - 0.388
South	0.039	-0.191 - 0.269
West	-0.040	-0.319 - 0.238
Health Plan type (reference: comprehensive health plan)		

HMO	0.053	-0.289 - 0.395
POS	0.084	-0.334 - 0.502
PPO	0.121	-0.152 - 0.395

DCG/HCC= Diagnostic Cost Group Hierarchical Condition Category; SSRI=selective serotonin reuptake inhibitor; NSAIDS=non-steroidal anti-inflammatory drug; Cox-2=cyclooxygenase-2; HMO=Health Maintenance Organization; POS=Point of Service; PPO=Preferred Provider Organization

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